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THE USE OF THE RICE DIET IN THE TREATMENT OF HYPERTENSION IN NONHOSPITALIZED PATIENTS*

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THIS report covers the first six months of a study of a group of ambulatory or nonhospitalized patients with hypertension who were treated with the rice diet. With the work of Kempner[1-4] as a guide but unlike his series in which all but a few patients were initially confined to a hospital, our patients were not hospitalized. So far as possible, nothing was changed in the daily routine of the patient except the diet. If he was ambulatory and working, this activity was continued. Patients who, when first started on the regime, were inactive because of their illness, continued on this routine except for the diet until improvement, if it did occur, warranted a more strenuous life. Moreover, these people were all private patients, and we supervised their treatment, with exceptions that will be discussed later.

TABLE 1. *Use of Rice Diet in 67 Cases.*

DIAGNOSIS	NO. OF CASES
Hypertension with renal failure*	4
Cardiac failure with edema	3
Coronary-artery disease with marked angina and no hypertension	5
Coronary-artery disease with hypertension	1
Essential hypertension	55
Nonco-operative patients	18
Patients who developed coronary occlusion early in treatment and were excluded from series	3
Patients with essential hypertension available for study	34

*All these cases were failures.

Sixty-seven patients were originally started on the rice diet (Table 1). Of this number, 4 had hypertension with renal failure; 3 had cardiac failure with edema; 5 had coronary-artery disease with severe angina pectoris and no hypertension; 1 had severe coronary-artery disease with hypertension; and 55 had essential hypertension. The study and results in the group with essential hypertension largely constitute this report.

Of the 55 patients with essential hypertension who were started on the diet, 18 were excluded from the study because of nonco-operation. Some of these failed to return for subsequent visits after having been advised to follow the diet. Others, after a few days, expressed unwillingness to remain on the diet, and still others, who did not admit their dietary divergence, were excluded because their twenty-four-hour urinary chloride excretions (expressed as sodium chloride) were so high as to make it obvious that they were not adhering to the regime. Also, 3 patients developed coronary occlusion within the first few days or weeks after having been started on the diet and were therefore excluded. Thus, there were 34 patients with essential hypertension who co-operated and were considered satisfactory for the report.

TABLE 2. *Age and Sex Distribution of 34 Patients with Essential Hypertension.**

AGE	MALE PATIENTS	FEMALE PATIENTS
yr.		
30–39	1	0
40–49	5	6
50–59	5	10
60–69	2	5
	13	21
Systolic blood pressure of 150 or below after therapy:		
30–39	0	0
40–49	3	1
50–59	1	7
60–69	2	2
	6	10
Drop of 50 mm. or more in systolic and 20 mm. or more in diastolic blood pressure:		
30–39	0	0
40–49	0	2
50–59	2	2
60–69	0	2
	2	6

*The rice diet benefited a total of 24 patients, or 70 per cent.

These 34 patients had had well established, known hypertension for at least three or more years. Many of them had been under personal observation during this time; others had been under the care of other physicians. Of this number, 21 were

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women, and 13 were men. They varied in age from 35 to 69 years (Table 2).

Methods

Before being started on the diet, each patient had a physical examination that included an electrocardiogram, blood counts, urinalysis and determinations of twenty-four-hour urinary chloride excretion, blood cholesterol, blood urea nitrogen, total protein, albumin-globulin ratio and blood chloride. Each patient received a copy of the rice diet,* as devised by Kempner,[5] which contains in 2000 calories not more than 5 gm. of fat and about 20 gm. of protein derived from rice and fruit and not more than 200 mg. of chloride and 150 mg. of sodium:

> A patient takes an average of 250 to 350 gm. of rice (dry weight) daily; any kind of rice may be used provided no sodium, chloride, milk, etc. has been added during its processing. . . All fruit juices and fruits are allowed, with the exception of nuts, dates, avocados and any dried or canned fruit or fruit derivatives to which substances other than white sugar have been added. . . Usually no water is given and the fluid intake is limited to 700 to 1,000 cc. of fruit juice per day.

Supplementary multiple vitamins were added, usually 2 unicaps per day, and iron when the patient was menstruating. Modified diets were outlined, mimeographed and ready for the patients' use as soon as their condition indicated. Directions for collecting the twenty-four-hour specimen of urine were also printed. It was believed that it was necessary to see these patients in the early part of the regime at least every two weeks to collect the twenty-four-hour specimen of urine for urinary chloride determinations as advised by Kempner,[1-4] secondly, merely to establish the diet in some cases and, thirdly, as in most cases, to maintain the diet and keep it varied. Patients who were perhaps too ill at the time, who for some other reason were unable to report for a regular two-week checkup or who because of psychologic reasons were having difficulty following the regime were seen by a volunteer worker (M. B. R.) at regular intervals in their homes. She answered any question about the use and preparation of the diet, collected the urine and blood specimens, recorded the blood pressure and pulse and took an electrocardiogram when it was considered necessary. One of her important duties on these visits was reassurance to the patient, making it understood that in most cases the diet was effective, that it was not necessarily a permanent one and that although they might have periods of extreme weakness and fatigue, and even depression, they would soon feel better. This plan worked very well, and it is believed that many patients who would otherwise not have adhered to the diet followed the regime faithfully and even cheerfully.

All sedation and medication were withdrawn from these patients as soon as possible, especially from those who were taking sodium pentobarbital or phenobarbital. The patients were expected to remain rigidly on the strict rice diet for a period of three months unless a satisfactory drop in blood pressure occurred before that time. With some patients, because of their age or for psychologic reasons, it was necessary to modify the diet before the three-month period had elapsed. Patients who, during this period, had remained strictly on the diet and who also had satisfactory urinary chloride excretions but whose blood pressure did not show significant drop were considered "failures," and the diet regime was concluded.

The diet was gradually modified for patients whose blood-pressure readings dropped satisfactorily. The first modification was the addition of one egg once a week, half a cup of nonleguminous vegetables (carrots, broccoli, celery, cabbage, asparagus, beets, spinach and so forth), boiled without salt, once a day and, if desired, a cup of coffee or tea once a day, with sugar, but without milk or cream; no salt or fat was included in any of the modifications, all of which contained the amounts of rice specified above. The patient stayed on this regime for two weeks to a month. If the blood-pressure readings were satisfactory at the end of this time, 4 ounces of lean meat, fish, liver or chicken three times weekly was added to the diet, the egg being taken three times a week and the nonleguminous vegetable once a day. The meat or fish was boiled or broiled, without salt or salt-containing substances. At this time, some patients were allowed salt-free bread,† two slices daily. If progress was satisfactory after another month, the diet was again modified, to allow 4 ounces of meat and so forth as mentioned above at one meal daily, half a cup each of two nonleguminous vegetables, one egg, either boiled or poached, three times weekly, and a baked or boiled white or sweet potato twice weekly. The fourth modification of the diet‡ was advised only for those patients whose blood-pressure readings had remained satisfactory after having been on the third modification for a month. This addition consisted of one egg daily if desired,

*Breakfast consisted of 2 or 3 ounces of rice (uncooked weight) with sugar or honey, two thirds of a glass of prune juice, a baked apple and a baked grapefruit. At 10 a.m., half a glass of orange juice was included, with grapes and an orange. Lunch consisted of rice (as at breakfast) with sugar or honey, five eighths of a glass of orange juice, one split banana with six slices of apple, a good many raisins and a baked slice of fresh pineapple with a cherry in the center. At 3 p.m. half a glass of orange juice, dried soft peaches and an apple were taken. Supper consisted of the rice with sugar or honey, two thirds of a glass of orange juice and a fruit plate (apricot, four sections of grapefruit, four orange sections and four figs). At 9 p.m. half a glass of orange juice was taken.

†Through the courtesy of Mr. Herbert Carlough, this bread, which contains only flour, yeast, sugar, vegetable shortening, and water, was made available by the Betty Bakerite Company.

‡This consisted of 1 egg three times a week (boiled or poached), ¼ lb. of lean meat, fish, chicken or liver four times a week (4 ounces with one meal), a small amount of nonleguminous vegetable seven times a week (½ cup), a small amount of white or sweet potatoes seven times a week (½ cup), boiled, without salt and 1 slice of salt-free bread with each meal.

No fluids except those listed with the rice diet were included. Vitamins and iron were continued.

Other alterations on discretion of physician.

meat and so forth once daily, any of the nonleguminous vegetables as desired, and a baked or boiled potato each day.

The blood-pressure readings were always taken in the same manner. Three readings were taken at intervals of five or ten minutes with the patient in the recumbent position. A mercury sphygmomanometer was always used, and the readings taken from the right arm. An average of the three readings was considered the actual reading for that visit. In the beginning of the regime, the patients were seen every two weeks for an accurate check on the blood pressure and for collection of a twenty-four-hour urine specimen. Determinations of the blood urea nitrogen, blood chloride, total protein, albumin-globulin ratio and blood cholesterol were done at monthly intervals.

Results

All the patients lost weight during the first and second months. The amount of weight loss depended upon the weight initially, but a loss of 10 to 15 pounds during this period was not unusual. The average weight of the patients was 155 pounds at the beginning, 146 pounds six weeks later and 144 pounds after three months — an average loss of 11 pounds per patient (Fig.1). Although after six months the average weight of the group was only 139 pounds, it did not mean that the patients were continuing to lose weight during the entire period, but rather that the failures had been excluded after three months. None of these patients were obese. In this series, the obese patients failed to co-operate.

The urinary chloride determinations averaged 8.6 gm. before the diet was started. This dropped rapidly, going below 1 gm. within the first two weeks and less than 0.5 gm. within the first six-week period (Fig. 1), and in some patients as low as 0.1 gm. As the diet was modified, the urinary chloride began to rise, reaching an average of 1.10 gm. shortly after the three-month period, and 1.31 gm. at the end of the six-month period.

The blood-pressure readings in the patients with essential hypertension averaged 210 systolic, 120 diastolic, before the regime was started, the highest being 260 systolic, 160 diastolic, and the lowest, 190 systolic, 102 diastolic. At three months, the average figure read 158 systolic, 100 diastolic. The same average figures were obtained at the end of the six-month period.

The systolic blood pressure dropped to 150 or below and the diastolic to 100 or below in 16 patients (10 women and 6 men). The blood pressure dropped 50 or more systolic and 20 or more diastolic in 8 patients (2 men and 6 women) (Table 2). Twenty-four patients, or 70 per cent, showed a definite and persistent drop in blood pressure.

The lowest readings were observed between the sixth week and the third month of the regime, while the patient was on the strict rice diet. As the diet was modified, a slight elevation of the blood pressure was observed, but in none of the successful cases did the pressure return to its original level.

The blood-pressure figures show no change from those obtained at the end of the third and sixth months, although the 10 cases of failure were excluded from the study after the three-month period (Fig. 1). This is explained by the fact that the average blood-pressure readings in the successful group were lower at the three-month period while the patients were on the strict rice diet than

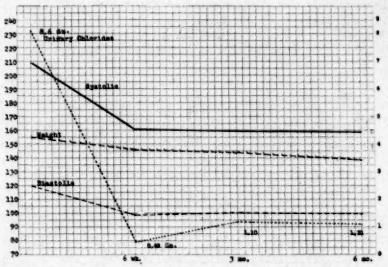

Figure 1. *Blood-Pressure Readings in 34 Cases of Essential Hypertension (including Failures).*

at the sixth-month period after the diet had been modified.

The blood chemistry was determined in each case every month for the first three months. None of the patients showed any change, with the exception of a decrease in the average cholesterol concentration in some cases. None of the patients observed developed a sodium or a chloride deficiency. During the hot summer months, these patients suffered no more from the heat than persons on normal diets. As a matter of fact, several of them maintained that they had a better summer than they had had in years.

All the patients experienced a period of weakness, which generally occurred from about the tenth to the twenty-first day and in some cases was even accompanied by a psychologic depression that required much understanding on the part of the physician and the volunteer worker. This period was only temporary, however, lasting at the most two or three weeks, and although no change was made in the diet, the patient began to feel stronger, and because of the reduction in blood pressure and absence of symptoms, all the patients felt increasingly better — far better than they had felt before the diet. It was very gratifying to find an absence

of headaches, when they had been the predominating complaint, much less tension and nervousness; these people were finally able to relax, rest and sleep well without sedation.

Case Reports

Case 1. V. L., a 49-year-old man, was first seen in 1937 for an unrelated illness. At this time, his blood-pressure reading was 130/80 (Fig. 2). The patient was seen at various intervals, but it was not until some time in 1943, when his chief complaint was severe headache, that he was found to have hypertension, with a reading of 190/110. He was admitted to the hospital, where all findings were normal except for hypertension. During subsequent years, his blood pressure continued to be elevated. On April 5, 1947, when it was found to be 220/120, he was placed on the rice diet. One month later, his blood pressure was 180/120, and the headache had somewhat abated. His blood pressure continued to drop, and on June 14 it was 140/95. He was started on the second modification of the diet and was advised that he could eat one slice of salt-free bread with each meal, but through some misunderstanding ate regular bread. When he was next seen on September 20, his blood pressure had risen to 160/100. The patient, at his next visit on December 13,

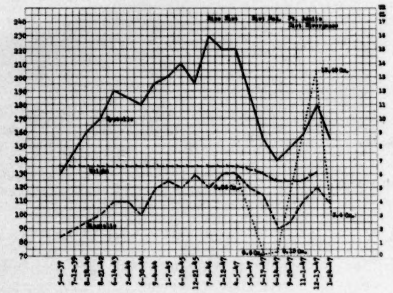

Figure 2. *Blood Pressure and Other Data in Case 1.*

admitted to irregularities in his diet, which were quite obvious. His blood pressure had risen to 180/120, and the urinary chloride excretion, which had been 3 gm., was now 13.48 gm. He had also had a recurrence of severe headache. He was advised to return to his diet, which he did, and when he was last seen on January 24, 1948, his blood pressure was 155/110, and the urinary chloride excretion was 3.48 gm. His headache had again disappeared.

Case 2. R. M., a 45-year-old woman, was first seen in 1945. She had been admitted to the Peter Bent Brigham Hospital for a surgical condition in 1943, when her blood pressure was 164/118. In the intervening years, her blood pressure varied from 180/96 to 200/115 (Fig. 3). She was readmitted to the hospital for study of the hypertension in April, 1946, when her blood pressure was 180/100. All other findings were normal and she was discharged. On December 26 her blood pressure was 190/110. She was started on the rice diet on June 24, when her blood pressure was 204/110. From this date, her blood pressure dropped spectacularly. On July 24, 1947, it had decreased to 150/85, and she had lost 13 pounds from her former weight of 153 pounds. Because of this favorable response, she was allowed the third modification of the diet. During a vacation, she indulged in food other than the diet, and on September 18, her blood pressure was found to be 155/92 and her urinary chloride excretion, which had been below 1 gm., had increased to 4.5 gm. She was again placed on the strict rice diet, and by January 6, 1948, her blood pressure had decreased to 135/86, and the urinary chloride excretion to 0.4 gm.

Case 3. A. P., a 65-year-old woman, was first seen in June, 1943, when her blood pressure was 210/110, with a history of known hypertension for 10 years before this visit. Her

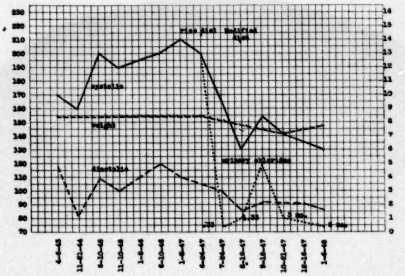

Figure 3. *Blood Pressure and Other Data in Case 2.*

main complaint was a "pressure band" across the back of her head, which she stated had been present for approximately 15 years. A period of rest and small doses of phenobarbital were advised. At yearly examinations, her blood-pressure readings varied between 198/118 and 230/130. In June, 1947, her blood pressure was 230/130, and she was started on the rice diet. After 2 weeks, her blood pressure was 180/110. After 6 weeks on the diet, her blood pressure had decreased to 150/90, and she felt much improved. She no longer complained of the pressure sensation in her head. Upon her next examination (August 16, 1947), her blood pressure was 130/90, and she was placed on a modified diet, which included meat, fish, vegetables and salt-free bread. The patient looked and felt markedly improved, and was capable of much more physical exertion than she had been for years. On September 16 her blood pressure was 150/100. These

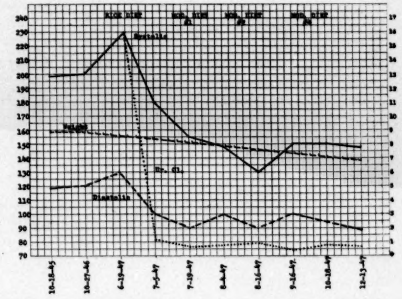

Figure 4. *Blood Pressure and Other Data in Case 3.*

figures have been maintained (Fig. 4), and although her diet has been modified to allow meat, vegetables and salt-free bread each day, the urinary chloride excretion has remained below 0.7 gm.

Case 4. T. R., a 53-year-old woman with known hypertension since 1937, was first examined in 1943, 6 months after

a cerebral accident with left-sided hemiplegia. At this time, her blood pressure was 230/150. Kidney-function tests were negative, and she had no cardiac symptoms. She weighed 180 pounds and was advised to go on a diet. During the following year she lost 15 pounds, with only a slight decrease in blood pressure. She was started on the rice diet on April 20, 1947, when her blood pressure was 190/140 and the urinary chloride excretion was 11.8 gm. Two months later, her blood pressure had decreased to 138/102, and the urinary chloride excretion to 0.103 gm. The diet was modified at this time, and despite an elevation of the urinary chloride excretion, her blood pressure has remained satisfactory (Fig. 5). When she was last examined on December 13, 1947, the blood pressure was 142/105.

CASE 5. F. G., a 69-year-old man, demonstrated a rapid drop in blood pressure and urinary chloride excretion with a subsequent rise in both after the diet was modified. When first seen he had a blood pressure of 220/110 and a urinary chloride excretion of 11.65 gm. During the previous 6 months, he had experienced precordial pain, suggestive of angina pectoris, and breathlessness on exertion. Kidney-function tests were negative. Although the patient was not working he was ambulatory, and no other change in his routine was prescribed with the exception of the rice diet. Ten days later, his blood pressure had decreased to 174/92, and the urinary chloride excretion to 0.79 gm. On November

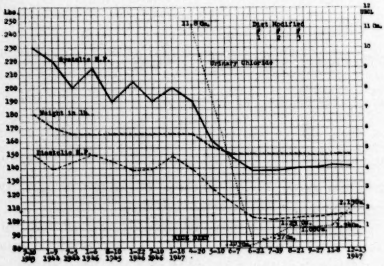

FIGURE 5. *Blood Pressure and Other Data in Case 4.*

18, 1947, his blood pressure was 128/80, the urinary chloride excretion was 0.20 gm., and the patient had lost 14 pounds. The diet was modified at this time, and on December 30, his blood pressure was 148/85, and the urinary chloride excretion was 2.08 gm. The chart on this patient ends with the December date (Fig. 6). However, he has been checked twice since that time, which brings his record up to a six-month interval. On February 24, 1948, the blood pressure was 150/84, and the urinary chloride excretion was 4.77 gm. On April 7, when the patient was last seen, the blood pressure was 176/92, and the urinary chloride excretion was 4.31 gm. Although this patient admitted to some slight deviations from his diet, which might very well account for the increase in the urinary chloride excretion, it was decided to allow him to continue on the modified regime since he was feeling so much better and had returned to work.

DISCUSSION

The rice diet has been found to be a practical, inexpensive and simple method for reducing blood pressure. It requires, however, understanding and co-operation on the part of the patient to maintain it strictly, since it is a rigid departure from what is usually considered a "normal" diet. Nevertheless, of the total number of patients who have been advised to go on the rice diet, the number of those who have refused to co-operate has been relatively small.

All the patients lost weight more or less markedly during the first ten to twenty days, depending on their initial weight and the amount of edema present (Fig.1). In most cases, the loss of weight was welcomed and, at a certain place in the regime, became stabilized. Patients who were

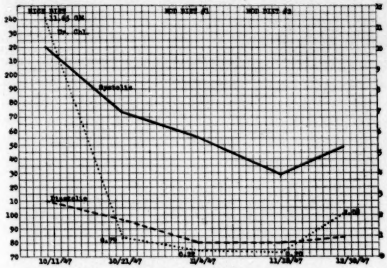

FIGURE 6. *Blood Pressure and Other Data in Case 5.*

underweight initially lost less than those who were overweight, but this condition likewise became adjusted as the routine progressed. It is my opinion that loss of weight has little or nothing to do with a drop in blood pressure, for several of the patients who were overweight had formerly been placed on low-calorie diets, and their blood pressure had not measurably altered. On the subject of weight loss, Kempner[1] has the following to say:

> It is not unusual for the weight to decrease more or less markedly during the first twenty days. The reason for this weight loss may be that the amount of food given does not cover the caloric requirements; in such cases, the amount of food must be increased, unless reduction of weight is indicated. Another reason may be that the patient does not eat the full amount of his diet during the first period of adjustment. The most frequent cause is the loss of visible edema; one patient with marked edema, for example, lost 63 lbs. within the first sixteen days on the diet.

Urinary chloride determinations done before the patients were started on the diet averaged 8.6 gm., the lowest being 3.2 gm. and the highest 13 gm. The great majority who adhered strictly to the diet had an excretion of less than 1 gm. after the first two weeks. At the end of one month, the determinations were between 0.2 and 0.15 gm.

Too much emphasis cannot be placed on the necessity for obtaining the urinary chloride determinations at two-week intervals. Aside from the value to the physician, scientifically, it is a valuable psychologic aid in maintaining the patient on the strict rice diet. Since it is obviously natural for patients to desire other food than that prescribed, it is carefully explained that any deviation from the

strict diet will be easily observed in these tests. This advice, in my experience, has proved an inhibitory factor in some patients whose need and desire for a varied menu was greater than that in others.

I have learned many things from my experience with a rather large number of patients on this diet. One of the most conspicuous problems is that it is difficult if not impossible to have a patient revert to the strict rice diet if the results on the modified diet have proved unsatisfactory. In the future, it will be necessary to maintain certain patients for a longer period on the strict rice diet. Also, the modified diets have been considerably altered to eliminate eggs, liver and certain nonleguminous vegetables high in sodium content — notably, spinach, beets and kale. The new modified diets add considerably less in quantity at each modification, and there are six diets instead of four. The results of these changes will be discussed in a subsequent publication.

Although these observations cover a limited period, it is my belief that the rice diet for hypertension offers the greatest hope so far for the medical treatment of a disease in which, to date, the therapeutic results have been notoriously poor.

The mechanism through which the reduction of blood pressure is achieved is not known, but it is difficult to escape the notion that the sodium ion[6–8] plays a role in a manner not yet clear.

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THYROID THERAPY IN GYNECOLOGIC ABNORMALITIES*

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FOR a number of years it has been the impression of obstetricians and gynecologists that lack of thyroid activity has a definite influence on the production of menstrual and obstetric abnormalities.

It has been said that "the relation of the thyroid gland to the sex organs is the most ancient and classical interrelation of the functions of the glands of internal secretion. Known to the ancients and a subject of daily gossip, it has passed down through the ages."[1]

In 1926 Litzenberg[2] noted the frequency of low basal metabolic rates in patients complaining of sterility and menstrual abnormalities, and in 1929 Litzenberg and Carey[3] reported 91 cases of sterility with low basal metabolic rates in 52. Of these, 36 per cent had abnormal menstruation, and 30 per cent conceived after thyroid medication. There were 2 abortions. Somewhat similar results were published by Haines and Mussey[4] in 1935 on 74 cases, some of which had been reported before, with menstrual abnormalities and low basal metabolic rates but no evidence of myxedema. This type of case has come to be known, correctly or not, by the name of "subclinical hypothyroidism."

Of their 74 patients, 59 complained of amenorrhea or oligomenorrhea, and 15 of menorrhagia. The basal metabolic rates varied in these patients, but none were less than —30 per cent and no patient had symptoms of myxedema. The resumption of normal menstruation following thyroid therapy occurred in about 60 per cent of patients with hypomenorrhea and in 53 per cent of those with menorrhagia.

It will be noted that 80 per cent of the menstrual abnormalities in these patients consisted of a decrease in menstrual activity as measured by amount, duration and frequency of menstrual flow.

On the other hand, Mason[5] found, in patients with so-called "subclinical hypothyroidism," frequent abnormal menstruation rather than actual amenorrhea, and Hamblen and his co-workers,[6] although finding no significant change in the actual bleeding from secretory endometrium in hypothyroidism, noticed a greater infrequency of menstrual periods. In discussing the apparent increased incidence of abortion in hypothyroid patients, the authors speak of the possible gametopathic effect of lowered oxygen metabolism due to lack of thyroid activity.

In discussions of papers in the gynecologic-endocrine literature it has become almost a common-

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place to state that thyroid medication is still the only trustworthy and efficacious hormonal preparation available for the treatment of menstrual disturbances. Furthermore, it is the general opinion of many gynecologists that the menstrual disturbances of hypothyroidism are those of hypomenorrhea — that is, absent or decreased menstruation — rather than profuse menstrual flow. On the other hand, the impression that decreased thyroid activity results in menorrhagia is a common one among internists, and Means[7] states this to be so in discussing menstrual abnormalities and diseases of the thyroid gland. In the same textbook, however, he quotes the observation of Ha[illegible]s and Mussey that hypomenorrhea is four times more frequent than hypermenorrhea in "subclinical hypothyroidism."

In an effort to determine experimentally the effect of hypothyroidism on menstruation, Engle[8] carried out thyroidectomies on 3 monkeys that had previously had normal menstrual cycles. Amenorrhea occurred in hypothyroid monkeys with intact ovaries, normal cyclic menstruation being reestablished by thyroid administration.

Since there is some question regarding not only the actual clinical entity of this group of patients who have slightly low basal metabolic rates and menstrual abnormalities but also just what their menstrual abnormalities are, it was decided to review a number of cases from the Sloane Hospital sterility and endocrine clinic in an attempt actually to identify this type of clinical picture, to define it more closely and to evaluate the result of thyroid therapy.

A review and analysis were therefore made of 550 consecutive patients seen in the sterility and endocrine clinic of the Sloane Hospital for Women who had complained of sterility or menstrual abnormalities or both. In an effort to evaluate the effects of thyroid therapy on the symptoms only patients who received thyroid medication were considered in this review. One hundred and fourteen patients, or 20.7 per cent, had received medication in addition to thyroid, so that they could not be considered in the results. Fifty-three of these cases were not followed. Sixty-one patients, or 11 per cent of the original 550, had received thyroid medication exclusively, and their progress had been sufficiently observed to warrant accurate conclusions about results. Their classification accord-

TABLE 1. *Classification of Patients According to Diagnosis and Basal Metabolic Rate.*

DIAGNOSIS	BASAL METABOLIC RATE			TOTALS
	NO. OF CASES 0 to −10%	NO. OF CASES −11 to −20%	NO. OF CASES −21 to −30%	
Sterility	11	11	2	24
Hypomenorrhea	9	9	5	23
Hypermenorrhea	2	2		4
Dysmenorrhea	1	5		6
Habitual abortion	1	3		4
Totals	24	30	7	61

TABLE 2. *Primary and Secondary Gynecologic Complaints and Results of Treatment with Thyroid.*

COMPLAINT	NO. OF CASES	COMPLAINT CORRECTED		FULL TERM PREGNANCY		ABORTIONS	
		NO.	PERCENTAGE	NO.	PERCENTAGE	NO.	PERCENTAGE
Sterility:							
Primary complaint	24	—	—	10	41.6	1	—
Secondary complaint	9	—	—				
Totals	33			13		2	—
Average					39.4		
Hypomenorrhea:							
Primary complaint	23	16	70.0	—	—	—	—
Secondary complaint	27						
Totals	50	31		—	—	—	—
Average			62.0				
Hypermenorrhea:							
Primary complaint	4	4	100.0	—	—	—	—
Secondary complaint	1						
Totals	5	5		—	—	—	—
Average			100.0				
Dysmenorrhea:							
Primary complaint	6	5	83.3	—	—	—	—
Secondary complaint	5						
Totals	11	9		—	—	—	—
Average			81.8				
Habitual or threatened abortion:							
Primary complaint	4	—	—	4	100.0		
Secondary complaint	3						
Totals	7	—	—	6			
Average					85.7		
Total primary complaints	61	39	(63.9)	—	—		
All complaints	106	64	(61.3%)	—	—		

ing to diagnoses and basal metabolic rates is presented in Table 1. Serum cholesterol studies were made in 35 of these patients. Of these, only 6 were above 225 mg. per 100 cc.

It must be stressed that these patients were actually a selected group in that they were given thyroid medication during their course of investigation and treatment in the clinic. It is therefore assumed that the clinician who saw them believed that thyroid medication was indicated. The great majority of the 550 cases reviewed did not receive thyroid therapy. This is especially significant in the small groups in this series, such as the cases of dysmenorrhea and habitual abortion. Most patients with similar complaints were treated by other technics so that the few who fell into the category of thyroid-treated cases are thought to have more significance than their numerical paucity admits.

The results of thyroid therapy are shown in Table 2. It would be incorrect to ascribe all pregnancies and all cures in these different groups to thyroid therapy alone. Certainly, in the cases of sterility there must be a certain percentage of patients who would have become pregnant during the course of investigation without any therapy whatever (3 out of 13 in a recent series of 52 cases of sterility). However, the patients placed on thyroid therapy had all finished their investigation, and the sterility had lasted from fourteen months to ten years.

Of the menstrual abnormalities it is certainly true that spontaneous remissions — or resumption of menstruation in cases of amenorrhea — occur, and undoubtedly a certain percentage of these patients would have spontaneously resumed normal menstruation. Most of them, however, had received therapy of various sorts elsewhere or in our clinic without success before receiving thyroid.

Table 3 compares our results with those reported elsewhere. It will be seen that for the most part the figures are fairly comparable.

Discussion

The cases presented add corroborative evidence to the impression long held by physicians treating menstrual disturbances: that there is a fairly common condition of mild thyroid deficiency, usually known as "subclinical hypothyroidism," that is amenable to thyroid therapy. This condition, which is sort of "twilight zone" between the normal gland and a state of myxedema, is characterized by symptoms suggestive of decreased metabolic activity such as weight gain, lassitude, dry skin, brittle fingernails, coarse hair and, what is most important to gynecologists, menstrual abnormality — decreased menstrual activity in the great majority of cases. Furthermore the basal metabolic rates and blood cholesterol determinations are, for the most part, not significantly abnormal.

Not the least of the significant relations between possible thyroid deficiency and this type of case is the appreciable number of patients improved by thyroid therapy. Not only in this series but also in others previously reported, there has been a fair percentage of cures in patients who received thyroid therapy only. This is especially true in the series of cases of sterility.

It seems legitimate to conclude, therefore, that thyroid therapy is advantageous in many cases of abnormal menstruation and sterility even in the presence of fairly normal basal metabolic rates. These patients do not have signs of myxedema and tolerate fairly large dosages of thyroid.

Table 3. *Thyroid Therapy in Gynecologic Abnormalities.*

Series	Sterility			Menstrual Abnormalities				
	Total No. of Cases	No. of Pregnancies	No. of Abortions	Total No. of Cases	Cases of Hypomenorrhea	Cures	Cases of Hypermenorrhea	Cures
						%		%
Litzenberg and Carey[3] ..	52	17 (30.0%)	2	—	—	—	—	—
Haines and Mussey[4]	—	—	—	74	59	60	15	53
Buxton and Vann	33	13 (39.4%)	3	55	50	62	5	100

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TRAUMATIC PARTIAL LOBECTOMY FROM GUNSHOT WOUND*

Report of a Case with Recovery and Personality Change

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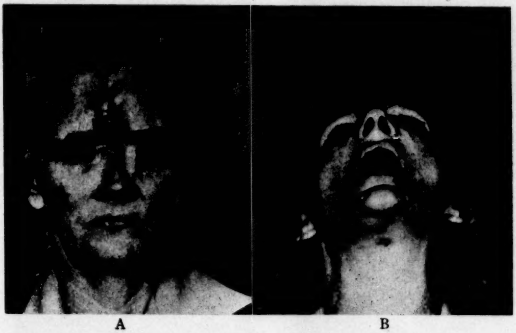
BOSTON

IN THE FOLLOWING case the patient received a head injury similar to that in the famous crowbar-skull case, which has been written up in the past and the skull of which is on exhibition at the Harvard Medical School Museum. In that case, a miner while tamping a hole in the ground filled with blasting powder accidentally ignited the blast, which created a projectile of the tamping crowbar. The projectile entered the head just lateral to the angle of the left ramus of the mandible, traveling medially and superiorly to find its exit near the midline, where the parietal and frontal bones meet. This man, after a stormy convalescence, lived for thirteen years and was able to go about the country as a living exhibit of this most unusual accident and injury. The only residual lesion that was noticeable to others was a changed personality consisting of increased profanity, obstinacy and fitfulness. In the last year of his life, the patient developed convulsions followed by others and death at thirty-eight years of age.

CASE REPORT

A 45-year-old woman had a pyramiding depression, which terminated in a suicidal attempt. To execute this, she held a 12-gauge shotgun under her chin and pulled the trigger. She was found in an unconscious state with a hole of entry in the midline of her chin about 1.5 cm. behind the symphysis. The hole carried up through the tongue, causing torn lacerations together with areas of complete loss of substance of that organ. It continued through the hard palate, the perpendicular plate of the ethmoid, both nasal bones, the frontal sinuses and part of the frontal bone as far as the hairline (Fig. 1). Some of the forehead scalp was lost. After débridement and the use of penicillin, the patient gradually recovered.

On admission to the Massachusetts Eye and Ear Infirmary, examination revealed that the frontal defect had granulated and epithelized over and was pulsating from the underlying brain. The forehead flaps had retracted laterally. A scar left in the soft tissue of the chin had closed over the floor of the mouth. The tongue had three points, and as a result of the laceration and scarring, it was bound down and immo-



A B

FIGURE 1. *Appearance of the Patient on Admission.*

A shows an area in the forehead covered by irregular epithelium beneath which there is scar tissue without dura, the brain being directly beneath. There is moderate loss of forehead skin associated with retraction of the remaining tissue. (Note the displacement of the left ascending process of the superior maxilla and the lacrimal bone with a slightly visible divergence of the pupil.) The nasal bones are absent. There is a hole in the nose. B demonstrates a point of entry in the soft tissues of the chin that has closed itself. In the palate is visible the hole that was shot out. On the forehead, the depression can be seen.

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bile. It was with much difficulty that the patient could talk or eat, since her tongue could not be pulled up to the roof of her mouth. The hole in the palate remained patent and

FIGURE 2. *Anteroposterior View of the Skull, Showing the Loss of the Frontal Sinus and Part of the Frontal Bone. Note the dispersed, small, lead shot.*

round but was closed by an upper plate. The membrane had healed over the anterior and posterior remaining parts of the septum, but there was a hole where the nasal bones should have been, with a depression to the level of the inner canthus. The left ascending process, lacrimal and ethmoid bones were pushed laterally, causing a marked diplopia (Fig. 1a).

A psychiatrist believed that the patient was perfectly oriented, without a psychosis, and that she had probably performed a partial anterior lobectomy, which had cured her pyramiding depression. Her vision was within normal limits; there had been no change after the accident other than a small tear in the right choroid.

X-ray study revealed the losses mentioned above. In addition, there were some pellets that had sprayed into the brain, one going back near the occiput (Fig. 2).

The corrective problems in this case were sevenfold: the brain needed protection; the hole into the nose should be closed; the hole in the palate should be closed; the function of her tongue would improve if the fragments were joined into one and the tongue freed so that the patient could talk

FIGURE 4. *Correction of the Lacerated, Bound-Down Tongue. A represents an anterior top view of the tongue. (Note the central scarred, bound down and immobile tongue with the three prongs of tissue — much of the tongue was shot away.) B is a diagram of the under surface of the tongue, revealing the incisions and the raw area just after removal of much of the scar tissue and freeing of the tongue. C shows the method of closure of the undersurface.*

and eat with greater ease; the displaced ascending process of the left superior maxilla, the lacrimal bone and the ethmoid should be brought back in the midline in an attempt to enlarge the orbit and thus permit the eye to have a normal range of excursion and probably lessen some of the diplopia; the contour of the nose and forehead would be improved if brought out to their original level; and the left lacrimal sac must be opened and drained into the nose to correct tearing.

All operative procedures were conducted under local anesthesia except the one in which bone grafting was done, and this was performed with a general anesthetic (nitrous oxide, oxygen and ether).

The first stage consisted of exposure of the displaced left superior maxilla and ethmoid bones, which were then freed and placed back into normal position. At the same time, the forehead wound was closed, the epidermis that had grown over the brain being removed and the brain being covered with forehead flaps, which were freed so that they could

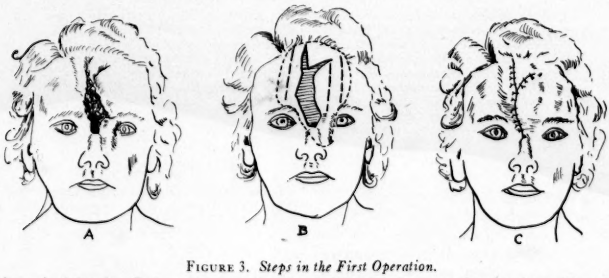

FIGURE 3. *Steps in the First Operation. A shows the deformity. B demonstrates the incision (solid line), the extent of undermining (short dotted line), and the incision through the aponeurosis (long dotted line). C shows the method of closure.*

approximate. The opening in the nose was partially closed by direct approximation of the skin edges (Fig. 3). A few days later, the scarred and bound-down tongue was mobilized, and the three points of the lacerated tongue were brought together. The scar on the undersurface was freed

The diplopia improved objectively, but the patient still has double vision though it is less pronounced. She also continued, after a couple of months, to have tearing and some infection in her left tear sac, so that a tear-sac operation was performed. As expected, there were no landmarks present,

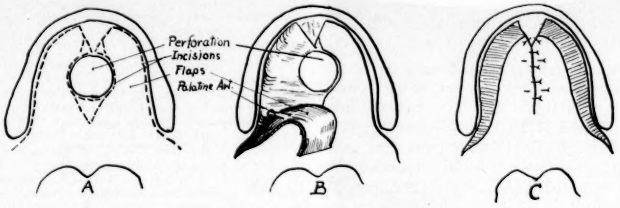

FIGURE 5. *Closure of the Palatal Defect.*
A shows the lines of the incision (heavy dotted line). In B one palatal flap has been raised, and the palatine artery exposed and stretched from its canal. C demonstrates the method of closure.

and corrected by a "Z" plasty. This enabled the patient to talk and eat much more easily (Fig. 4). At a later stage, the hole in the palate was closed, two flaps being utilized, as in a case of cleft palate (Fig. 5). This further improved speech and facility in eating because the mouth was separated from the nose. The patient still had the hole through the dorsum

since the area of the lacrimal bone and sac were comminuted and filled with fragments of bone, callus and scarred tissue. What was left of the tear sac was freed, and this was opened and drained into the nose. Her tearing is less, and the infection has gone.

FIGURE 6. *The Postoperative Result.*
The forehead has been brought out to a normal contour. There is still some irregularity of the skin. The ascending processes and lacrimal bone and ethmoid are in place, and the nose is elevated. (Note the restoration of the nasal bones.)

of her nose and the depression caused by the loss of frontal and nasal bones. This condition was corrected by a bone graft taken from the ilium. It was unnecessary to employ skin grafting to obtain skin for the region of the glabella and the nasal dorsum (Fig. 6).

The patient is most appreciative of all that has been done for her and has resumed her place as an active member in her community.

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INFECTIOUS MONONUCLEOSIS WITH PSYCHOSIS*

Report of a Case

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INVOLVEMENT of the central nervous system in infectious mononucleosis has been reported by a number of authors since the patients with meningitis described in 1931 by Johansen[1] and by Epstein and Dameshek.[2] However, cases of infectious mononucleosis associated with psychosis have not appeared up to the present time in the literature to our knowledge. Many cases of meningitis and peripheral-nerve palsies, occurring separately or together, have been reported.[3–12] Bernstein's[13] monograph summarized most of these early reports up to 1940. In 1941, while publishing the details of a case of meningeal involvement, together with ataxia, catatonia and slurred speech, Landes, Reich and Perlow[14] reviewed the literature with particular regard to central-nervous-system manifestations. Since that time cases of a similar nature have been added to the literature.[15–26] All these patients had serous meningeal findings or some other neurologic manifestation such as paralyses, convulsions or reflex changes. At times the picture simulated a Guillain-Barré syndrome.

Because the condition is rarely fatal, only a few cases of infectious mononucleosis have come to autopsy. Particular examples are those reported by Ziegler,[26] Allen and Kellner[27] and Peters et al.[28] All pointed out a nonspecific but definite involvement of the central nervous system with increased vascular reaction of the pia arachnoid, petechial hemorrhages in the brain and degenerative changes of the Purkinje cells. The literature since Bernstein's article has been summarized twice by Bethell et al.[29, 30] In reporting 2 additional cases, Slade[31] completed a review of the literature up to 1946, which dealt with central-nervous-system involvement in infectious mononucleosis. In none of these reports can one find a case of psychosis associated with acute infectious mononucleosis.

The following case report is that of a psychotic episode resembling schizophrenia that occurred during the course of typical acute infectious mononucleosis and subsided during the regression of the disease.

CASE REPORT

E. T., a 25-year-old married college student, was admitted to the Albany Hospital on December 11, 1947. He was placed on the psychiatric ward because he had become unmanageable in a neighboring hospital. The history obtained from his family revealed that he had developed general malaise, anorexia, fatigue, headache, a temperature of 102°F. and sweating, but no chills, about 16 days prior to admission. Entering the referring hospital on December 1, he had complained that his symptoms had grown progressively worse and that he had developed painful lymph nodes in his neck with some abdominal discomfort. At that time, physical examination revealed a well developed and well nourished man who was alert and co-operative with a blood pressure of 120/70, a temperature of 98.6°F. and respirations of 20. Positive physical findings included injected scleras, a coated tongue, bilateral cervical lymphadenopathy in the posterior chain and several small inguinal lymph nodes. The rest of the physical examination was negative. Examination of the blood on December 1 showed a red-cell count of 4,800,000, with a hemoglobin of 90 per cent (Sahli), and a white-cell count of 4500, with 1 per cent basophils, 3 per cent eosinophils, 15 per cent stab forms, 20 per cent segmented neutrophils, 51 per cent lymphocytes and 4 per cent monocytes. Fifty per cent of the lymphocytes appeared large and abnormal. The urine was normal. On the 2nd day, heterophil-antibody agglutination was reported positive in a dilution of 1:40. Also a Widal test was reported positive in a dilution of 1:100 (the patient was a World War II veteran). No brucella agglutination was obtained.

On the fourth hospital day, repeated examination of the blood disclosed a red-cell count of 5,200,000, with a hemoglobin of 108 per cent (Sahli), and a white-cell count of 5900, with 2 per cent basophils, 1 per cent eosinophils, 10 per cent stab forms, 19 per cent segmented neutrophils, 61 per cent lymphocytes and 4 per cent monocytes. There were 2 young lymphocytes, and on this day heterophil-antibody agglutination was reported positive in a dilution of 1:60. On the 5th day the agglutination was positive in a dilution of 1:320. Examination of the spinal fluid showed a total protein of 15 mg. per 100 cc. An x-ray film of the chest on admission revealed an area of increased density in the region of the hilus that was consistent with peribronchial infiltration, but not suggestive of pneumonia or tuberculosis. The course of the disease from time of entry on December 1 until transfer to the Albany Hospital was reported as most disturbing mentally. Review of the record showed that the patient was confused much of the time from the day of admission. The nurses reported that he became more irritable, often was overtalkative and showed "flight of ideas" in speech. He was demanding at times and on one occasion attempted to walk out of the hospital. He became belligerent, impulsive and unpredictable in his behavior, and once he threw a glass of water in the nurse's face. He received penicillin and sedatives during his stay, but as time passed, he became delusional, his speech was rambling, and he talked of his sex life much of the time. Because of his behavior, he was transferred to the Albany Hospital.

Physical examination was only slightly different from that previously reported. There was a papuloerythematous rash on the back. The pharynx was injected, and there were dry patchy areas of denuded epithelium with a white exudate visible. The cervical lymph nodes were still enlarged but not tender. The remainder of the physical and neurologic examinations were completely within normal limits. The patient's mental status was definitely abnormal. He was overactive and overtalkative, impulsive and unpredictable. His thinking was rambling and irrevelant. He seemed preoccupied with thoughts of his family, childhood and health. No definite delusions or hallucinations were noted at this time, but his mood was often labile, and his affect seemed inappropriate. He was well oriented in time, place and person, but his insight and judgment were lacking.

The temperature was 101°F.

Urinalysis demonstrated a reaction of pH 6.5, a specific gravity of 1.020 and a trace of albumin. There was no sugar,

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acetone or urobilinogen, and microscopical examination was negative. Examination of the blood showed a red-cell count of 4,320,000, with a hemoglobin of 108 per cent (Sahli), and a white-cell count of 16,050, with 1 per cent stab forms, 24 per cent segmented neutrophils and 75 per cent lymphocytes. Many of the lymphocytes showed large amounts of pale-blue cytoplasm, with large oval nucleoli. The blood sugar was 91 mg., and the blood nonprotein nitrogen 35 mg. per 100 cc. The blood Wassermann test was negative. A heterophil-antibody agglutination was positive in a dilution of 1:1792. The spinal fluid was clear and showed no cells; the total protein was 42 mg., the chloride 760 mg., and the sugar 66 mg. per 100 cc. The spinal-fluid Wassermann test was negative, as was the colloidal-gold test.

The patient was treated symptomatically with adequate diet, fluids and sedatives. On several occasions he showed definite evidence of auditory and visual hallucinations and delusions. His behavior alternated from overactivity and excitement to withdrawal and loss of contact with his environment. The picture resembled an acute schizophrenic episode. On December 19 there was a dramatic change in his mental status. He became alert and co-operative. There was none of the overactivity or overtalkativeness. The delusions and hallucinations had completely disappeared. The temperature fell to normal on December 20 and 3 days later he was well enough to be discharged. The lymph nodes were still moderately enlarged, and the spleen was palpable three fingerbreadths below the costal margin. He was seen later for a follow-up examination, and no abnormality was found psychiatrically. The symptoms of infectious mononucleosis had subsided except for some fatigue. He went back to his college career and is doing very well, leading an active social as well as scholastic life, according to a report 3 months later. The clinical course is demonstrated in Figure 1.

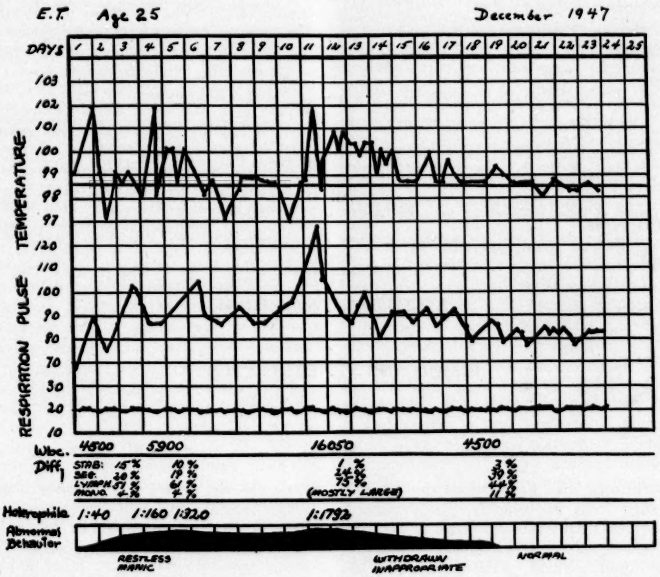

FIGURE 1. *Clinical Course.*

DISCUSSION

There was considerable controversy regarding whether this was a case of toxic psychosis associated with infectious mononucleosis, or whether there was an actual schizophrenia precipitated by the febrile illness. The diagnosis of infectious mononucleosis was certain in view of the fever, enlarged lymph nodes, abnormal lymphocytes in increased number and the rising titer of the heterophil-antibody agglutination. The absence of any neurologic manifestations, the failure to demonstrate pathologic changes in the cerebrospinal fluid, and the dramatic resolution of the marked psychotic episode suggested that a toxic psychosis was the best explanation of the syndrome.

SUMMARY

The literature relating to central-nervous-system involvement in infectious mononucleosis is briefly reviewed, and a case of this disease with a toxic psychosis resembling schizophrenia presented.

We are indebted to Dr. S. Eugene Barrera, neurologist and psychiatrist-in-chief, and to Dr. L. Whittington Gorham, physician-in-chief, Albany Hospital, for permission to report this case.

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MEDICAL PROGRESS

BLOOD AND ITS DERIVATIVES*

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SINCE prehistoric man first noticed the red fluid that issued from his wounds, much thought and energy have been expended toward the conservation, investigation and utilization of this life-symbolizing liquid — blood. The past decade has witnessed great advances along these lines impelled by the demands of the recent war. To summarize all aspects of this important subject, however, would involve a treatise on the major branches of medicine. This review is restricted to the following topics: whole blood — preservation, use, reactions, salvage of erythrocyte residues, physiology and procurement; plasma — homologous serum hepatitis and clinical use; plasma fractionation — methods, use of fractions and mechanism of action; blood substitutes; protein therapy — metabolism, administration and reactions; and laboratory methods — amino acids, total protein and protein fractions. One major subject — the Rh factor — is reserved for a separate review.[1]

It is intended that this will supplement previous reviews on blood and plasma proteins appearing in the *Journal* since 1941.[2–5] These form a helpful background for the following general discussion. More detailed information can be obtained from many excellent reviews now available.[6–18]

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BLOOD

Preservation

World War I initiated the use of blood transfusions on a large scale. Until World War II, however, technics changed little, and blood was given directly through a variety of devices or indirectly, sodium citrate being used as an anticoagulant.[19] The storage period of five to seven days permitted by this system was satisfactory for most hospitals, very few of which had banks, but it was totally inadequate for military use. Worldwide problems of logistics demanded a longer dating period and more stability. This difficulty was resolved early in the war by the development and use of dried plasma, dried serum and concentrated human serum albumin. Although these agents were extremely useful, increasing medical experience showed that no substitute approached the efficacy of blood in the severely wounded.[6] Accordingly, in 1944

the Committee on Medical Research of the Office of Scientific Research and Development and the Army and Navy medical departments took up again the problem of preserving and shipping whole blood. The findings of the six major groups of investigators recently appeared simultaneously.[20–31]

Studying the effects of variations in reaction, temperature, buffers, concentration of glucose and volume of diluent, it was generally agreed that maximal preservation followed the use of a slightly acid citrate-dextrose solution,* which was cooled to 4 to 10°C. before the blood was collected and maintained there continuously thereafter. A formula utilizing these principles had already been proposed by Loutit and Mollison.[32] Using erythrocytes tagged with radioactive iron (Fe^{55} and Fe^{59}) by feeding isotopic iron to donors, J. G. Gibson et al.[20, 21] were able to show that when blood was drawn as stated above, maintained at 4 to 10°C. for twenty-one days and then transfused, 70 to 80 per cent of the transfused cells were viable at least five days after transfusion. To achieve the same survival under comparable conditions, blood in a neutral citrate glucose solution (diluent volume equal to blood volume) could be stored only fifteen days, and blood in sodium citrate could be stored only one to four days.[28] If the temperature rises above 15°C. even once during storage, subsequent cooling fails to retard the rapid rate of deterioration thus initiated,[23, 28] though spontaneous hemolysis may not occur before transfusion. With 80 per cent survival, all the nonviable erythrocytes are removed from the circulation within twenty-four hours (most within two hours).[22, 28] All the iron from the nonvital cells is utilized to make new hemoglobin. Utilization is about twenty times that of equivalent amounts of iron given by mouth.

Although some thought a 7:3 blood:diluent ratio optimal,[26] the practical aspects of smaller diluent volume led to the development of an improved ACD formula using 75 cc. diluent for 500 cc. of blood,† and achieving equal preservation. Strumia et al.[31] report the satisfactory routine hospital use of 5000 bottles of blood preserved with this formula.

The same investigators,[21, 28, 30] studying the preservation of erythrocytes discarded from plasma preparation, agreed that the best survival resulted when blood was collected in cooled bottles and immediately separated, and the cells resuspended in ACD solution if collected in sodium citrate, or stored undiluted if collected in ACD and diluted with a little hypertonic saline solution just prior to administration; 80 per cent survival was possible after ten to fifteen days' storage by this method.

*Acid-citrate-dextrose solution (ACD-1) formula: sodium citrate ($Na_3C_6H_5O_7 \cdot 2H_2O$) — 1.33 gm. per 100 cc., citric acid ($C_6H_8O_7H_2O$) — 0.47 gm. per 100 cc., dextrose (anhydrous) — 3.00 gm. per 100 cc.; 25 cc. of the solution is used for each 100 cc. of blood.

†The revised formula of ACD-3 is as follows: $Na_3C_6H_5O_7 \cdot 2H_2O$, 1.60 gm. per 100 cc.; $C_6H_8O_7 \cdot H_2O$, 0.56 gm. per 100 cc.; and dextrose (anhydrous), 1.50 gm. per 100 cc.; 15 cc. of ACD-3 is used for each 100 cc. of blood.

Use

Whole blood was originally transfused to replace that lost by hemorrhage.[33] It was also found to be effective in traumatic shock even when external blood loss had been minimal. This is to be expected from the currently accepted theories that the shock is a condition of diminished cardiac output, depleted circulating blood volume and peripheral vascular collapse.[7, 8, 11] Evidence for and against a humoral or neurogenic origin, or both, is still confusing. Severe shock, however, often fails to respond to massive transfusions, thereby casting some doubt on the theory that deranged circulatory dynamics was the major physiopathology of shock. Seligman et al.[34] have sought to incriminate the liver. Perfusion of the liver by cross circulation with a donor dog (femoral artery to splenic vein) saved 8 of 9 dogs in standardized "irreversible" hemorrhagic shock, whereas femoral-artery to femoral-vein perfusion saved only 2 of 9 controls.

Seeking to make blood more effective, others have tried intra-arterial or intracardiac transfusions. Glasser and Page[35] revived 9 of 35 dogs kept in hemorrhagic shock for two and a quarter hours, then bled until pulse and respiration ceased and finally given intra-arterial blood and artificial respiration. Lefébure,[36] in France, was quite successful with intracardiac infusions of oxygenated blood in shocked cats or oxygenated intracardiac autotransfusions in drowned and electrocuted cats, drawing blood from the femoral vein, oxygenating it and giving it into the heart. He records the rumor that, using this method, Vladimir Negosky in Russia saved 12 of 51 soldiers considered otherwise lost. Iokhveds[37] reports 2 such cases, 1 of which was saved. Kay and Hacker[38] gave oxygenated blood into the ascending aorta and believed that a patient exsanguinated from a stabbed right internal mammary artery was saved thereby.

Two uses of transfusion, apart from shock treatment, have been featured recently. European workers[39] seem to believe that frequent small transfusions hasten convalescence from rheumatoid arthritis faster than the mere replacement of hemoglobin alone. Barsi[40] thinks this particularly effective if the donors are pregnant.

The most spectacular new use for blood has been the substitution therapy for erythroblastotic infants, reported by Wallerstein[41, 42] and others.[43] Since the newborn infant's total blood volume is only 250 cc., it is possible to infuse Rh— blood and withdraw the patient's blood simultaneously from a different vein for sixty minutes, leaving at the end only 36.7 per cent of the infant's blood in its circulation. Alternate removal and replacement of 50 cc. of blood five times reduces the residual blood to 32 per cent and the addition of 100 cc. of Rh— blood reduces this further to 25 per cent, thereby providing enough blood to live on until all the

circulating Rh agglutinins have been used up. Seven of 9 infants so treated were in satisfactory condition six months later. Wallerstein takes such infants off breast feedings, since Witebsky[44] has shown that it is possible to excrete Rh agglutinins in milk. Cathie,[45] however, denies that this is clinically significant.

Almost all blood is now given indirectly. Only one new device for direct transfusion has been described recently, and it is from Australia.[46]

Reactions

The usual reactions to transfusions — pyrogenic and hemolytic — are now considerably less frequent owing to more careful preparation of equipment, better crossmatching and the use of more potent grouping serums. Several other types of reactions merit closer attention.

Although *homologous serum hepatitis* is much more common after plasma than blood transfusions, it does occur with the latter. Two fatal cases are reported[47, 48] in infants fifteen to sixteen weeks old who had received three blood transfusions each sixty to one hundred days before, and a fatal case in an adult is reported from Argentina.[49] The most complete follow-up survey yet done included 1050 patients receiving blood or plasma, or both, and 891 receiving blood alone[50]; 7.3 per cent of the first group and none of the second were considered to have had hepatitis. Nevertheless, no one should be used as a donor who has had jaundice, been exposed to jaundice or received any injections of blood or its derivatives in the preceding six months.

A case of transfusion-induced quartan *malaria* is reported by Fischer and York[51] from Providence, Rhode Island, occurring in a native, unexposed New Englander receiving three transfusions from donors who had had malaria in early life but had been symptom-free and living outside an endemic area for thirty, thirty-six and forty-two years respectively. These authors report from the literature 12 other cases of transfusion malaria in Massachusetts between 1929 and 1944, 10 of the donors having previously lived in endemic areas, and 5 of these having been symptom-free more than twelve years. The bloods in this case had been stored at 6°C. for five, seven and twelve days. Coggeshall[52] also reports transmission from eight-day-old blood. It is important, then, to reject as donors all people who have ever had malaria, and if a would-be donor has lived in an endemic area or taken suppressive therapy, to wait at least two years[52] before use as a donor, and then only if no symptoms have developed. Even this procedure is not entirely safe, for Rogers[53] has recently reported a case of quartan malaria appearing in an eighteen-year-old London girl eight weeks after receiving one ante-partum transfusion from a donor who had lived five months in a malarious area seven years before but had never shown any clinical symptoms of infection.

An interesting observation on the use of the *universal donor* — Group O — was made during J. G. Gibson's[20] cell-survival studies. A Group A recipient given radioactively tagged O blood had 800 cc. of his own blood destroyed by the high anti-A agglutinin content of the donated blood. It was possible to show that the recipient's cells were the ones destroyed because there was no diminution in the number of tagged donated cells. A similar reaction, but with fatal outcome, is reported from England[54] in which a thirty-eight-year-old Group A man with a pistol shot wound received three transfusions of O blood, with severe hemolytic reaction and death from lower-nephron nephrosis. The donors were found to have anti-A agglutinin titers of 1:256, 1:512 and 1:4096. In the Red Cross, Army and Navy whole-blood program, 205,907 bottles of O blood were sent to the European theater and 181,555 bottles to the Pacific.[55] All blood had anti-A and anti-B titrations done, and the 20 per cent with the highest values were reserved for use in O recipients. The remaining 80 per cent had titers well below 1:64. Although a fair amount of pigment nephropathy and lower-nephron nephrosis was seen in North Africa and Italy — Snyder[56] reports 68 fatal cases in Fifth Army Hospitals in 1944–1945 — it was believed that this might well have been due to prolonged shock of severe degree before resuscitation rather than to the O blood. Perhaps this is true, since an analysis of 21,296 reports (part of the 171,564 bottles of O blood administered in the Pacific) failed to show any case with similar lesions.[57] (The total reaction rate in this series was only 3.1 per cent). If O blood is to be used for universal transfusion, it should have an anti-A and anti-B agglutinin titer of 1:64 or less, or Witebsky's[58] A and B substances* should be added before transfusion.

The *anuria* following hemolytic transfusion reactions has been treated[59] by the use of the artificial kidneys of Kolff[60, 61] and Murray[62] and the peritoneal irrigation of Frank, Seligman and Fine.[63] It is not yet possible to pass judgment on their effectiveness.

In the best Gallic tradition, Hustin and Rémy[64] studied transfusion-reaction rates in relation to *sex*. The over-all rate of 9.2 per cent for 864 transfusions given to 425 men and 439 women when broken down showed only 5.3 per cent reactions when donor and recipient were both

*These are complex carbohydrate-like compounds, free from protein, that seem to play an important part in the composition of isoagglutinogens and combine with isoagglutinins rendering them ineffective. Commercial preparations are obtained from pepsin, mucin, peptone, gastric juice, hog stomach and so forth.

men, and 17.3 per cent when both were women. When all donors were men the rate was 7.2 per cent, and when the sexes were mixed (man to woman or vice versa) the rate remained 7.7 per cent. The authors highly recommended the last procedure.

Salvage of Erythrocyte Residues

Apart from a limited use of erythrocyte transfusions in anemia,[65] valuable for their small volume, little progress has been made toward salvaging the large quantity of erythrocytes accumulating from a plasma or plasma-fractionation program. Early interest in red-cell pastes[66] or dried preparations as stimulants for wound healing has waned and is now reported chiefly from Europe.[67, 68]

Van Slyke and his associates[69–71] have reported their experiences with the preparation and use of dried hemoglobin for transfusions. Following earlier work,[69] they evolved the following method. Cells are laked with distilled water, stroma precipitated by bringing the reaction to pH 5.7, most of the potassium removed by exchanging for the sodium of sodium zeolite, zeolite and stroma removed by centrifuging, physiologic concentration and reaction achieved through the addition of sodium chloride and sodium bicarbonate, and sterility obtained by Seitz filtration. This gives a solution of 95 to 98 per cent hemoglobin in the active form with no conversion to methemoglobin in solutions kept two and a half months at 4°C. If 99.7 per cent deoxygenated, it is readily lyophilized without developing methemoglobin. This material stored in vacuum retains all its oxygen-binding properties for one hundred and eighty days at 4° to 30°C., ninety-two days at 38°C. and seven days at 56°C. After restoration in a vacuum, no methemoglobin is formed, and the material can then be kept in solution with impunity.

A 7 per cent hemoglobin solution was quite satisfactory for treating hemorrhagic shock in dogs.[71] A transitory depression in urea clearance in some of the dogs following hemoglobin treatment has led the Van Slyke group to recommend that hemoglobin not be used clinically until the significance of this is clarified. Since most reactions following hemoglobin administration have been shown to be due to methemoglobin[72, 73] and since this preparation contains practically no methemoglobin, stroma or lipids, it is quite possible that a safe, effective hemoglobin solution can soon be prepared.

Strumia et al.[74, 75] sought to avoid the dangers of methemoglobin and perfected a method for the preparation of modified globin. This is a moderately homogeneous preparation with a slightly asymmetric molecule weighing approximately 34,000[14] and having colloidal and nutritional properties quite similar to those of serum albumin. They concluded from studies on 7 surgical patients that globin could replace plasma in supplying protein needs.[76] The "doubly depleted" dogs (anemic and hypoproteinemic) of Robscheit-Robbins and her co-workers[77] used this human globin to form hemoglobin and plasma proteins though dog globin was better tolerated.

Physiology

The physiologic tagging of erythrocytes through the use of radioactive iron enabled investigators to study the *erythrocyte life cycle* in vivo as well as in vitro. The evidence from transfusion-survival studies[21] of a life cycle of one hundred to one hundred and twenty days (approximately 1 per cent per day disappearance) taken with the earlier results of Ashby and Wearn[78] using nonagglutinable cell technics, and Hawkins and Whipple,[79] who followed hemoglobin excretion, as well as the recent work of London, Shemin and Rittenberg,[80–82] who labeled the globin portion by feeding glycine containing N^{15}, leaves little doubt that normal erythrocytes have a life span of one hundred and ten to one hundred and thirty days. It is difficult to understand the results recently reported in Scandinavia[83, 84] of thirty to fifty days (the figures most frequently quoted before the war). Perhaps the reticulocytes and elliptocytes used in these careful studies do not behave as normal adult erythrocytes do.

The *sludged-blood* report released by Knisely's group[85] summarizes their work for the past sixteen years in an important aspect of physiology. They have observed and photographed[86] the circulation of thousands of intact and dissected animals and, using a binocular dissecting microscope and oblique illumination, have studied the corneal and conjunctival vessels of hundreds of normal subjects and patients. They found that in the healthy organism no fluid leaks through capillaries, there is no erythrocyte agglutination or phagocytic removal of red cells, and blood flow is faster in the center of a blood vessel, the cells moving in concentric tubular layers with plasma next to the intima. There are numerous acute bottlenecks at arteriolar-capillary junctions, since the capillaries are only slightly larger than the erythrocyte diameter. The bottlenecks and capillaries are extremely labile and capable of complete self-occlusion. Even during occlusion in normal animals fluid leakage did not occur unless the capillaries were forcibly dilated — in which case the proteins always leaked out. In almost all diseased states (over 600 unanesthetized patients), including mild sinusitis or colds, the leukocytes rolled along and stuck to the blood vessel walls, and many capillaries were dilated and leaking and were packed with erythrocytes stuck to each other quite firmly by a clear tenacious substance. These "sludges" frequently obstructed vessels for hours. Their moving pictures of normal and sludged blood in

color are most instructive and are available for viewing.[87]

Procurement

At present, whole blood is irreplaceable in modern therapeutics. To guarantee a continued supply in the quantities that came to be used during the war, several agencies have set up peace-time procurement plans. The National Association of Blood Donors in Italy seeks Government recognition.[88] The Ministry of Health in England supplies whole blood and plasma.[89] Besides the state blood and plasma programs of Michigan and New York[90] and the Massachusetts[91] program of whole blood and plasma fractionation, the American Red Cross initiated a nationwide peace-time procurement program in November, 1947.[92] Opening their first center in Rochester, New York, at that time, they hoped to establish twenty to twenty-five more this year, and in three to five years they plan to collect three million donations annually. This is in collaboration with existing state and local facilities and is to provide blood for transfusions, fractionation and research, all free of charge.

Plasma

Homologous Serum Hepatitis

The brilliant wartime career of plasma is now a well known and well documented story.[11, 93] Suggested by Ward[94] in 1918, first used by Filatov[95] in 1935 and reported in this country since 1938, this therapy became very popular with the establishment of plasma and serum programs in Britain and America to meet wartime needs. The details of collection, preservation and use need not be recounted again.[11] Having played an irreplaceable role in war medicine, plasma therapy now faces a serious threat to its future use — the danger of transmission of homologous serum hepatitis or jaundice. First reported in 1937,[96–99] this disease was thought to be of little consequence until, with more general use of plasma, larger pools and more donors, it was observed with increasing frequency in Britain and later in the United States.

The widespread use of plasma, the transient character of military-hospital populations and the long incubation period of the disease have seriously limited attempts to estimate the *incidence* of hepatitis following blood and plasma transfusions. The most complete survey yet reported is by Spurling, Shone and Vaughan.[50] They followed all patients surviving at least four weeks after receiving serum or plasma in 78 northwest London hospitals from 1940 to July, 1945, all receiving blood from January, 1944, to July, 1945, in 23 of these hospitals, and an equivalent number of controls matched as nearly as possible according to age, sex, ward and hospital but who received neither serum nor plasma. The authors were able to communicate with or study adequately 1054 of the 2040 receiving serum and plasma and 891 of the 1284 receiving blood alone (these patients received 2278 of 2468 bottles given). The serum-plasma group revealed 77 cases suggestive of homologous serum jaundice (7.3 per cent) and 1.3 per cent with jaundice of other origin. None of the blood recipients or the controls had jaundice in five months.

On June 1, 1945, the United States Army conducted a hepatitis survey in all its general hospitals in the United States.[100] Of 1762 patients with jaundice on that day, 500 gave a history of recent transfusions with blood or its derivatives. In the preceding thirty days, 9 of 15 patients dying of jaundice had been transfused previously.

Scheinberg et al.[101] followed 2443 transfusions from the blood bank of the Peter Bent Brigham and Children's hospitals in Boston between August, 1944, and August, 1945, and found 11 cases (0.45 per cent) of hepatitis, including 4 deaths.

Brightman and Korns[102] followed 649 recipients of surplus Army and Red Cross plasma in New York state and found 4.5 per cent hepatitis, with no hepatitis in 1597 household contacts (therefore, it was unlikely that the hepatitis was infectious). In six months 51 deaths from acute hepatitis were reported; 15 of these patients had been previously transfused, 12 with plasma alone.

Rosenthal[103] gave 695 units of blood and plasma to 98 patients in ten months with 4 cases of probable serum hepatitis (none with blood alone).

Grossman and Saward[104] from September, 1943, to September, 1945, had 8 cases of hepatitis (including 1 fatal case) in 501 infusions of commercial liquid plasma. Ginsberg[105] reported a fatal outcome in 2 of 14 cases.

Three cases following the administration of blood alone were discussed above.

A method of *destruction* of the etiologic agent has been reported in only one study. Wolf et al.[106] passed plasma in a thin, rapidly moving film under an Oppenheimer–Levinson source of ultraviolet radiation of 2537 angstrom units and 1849 angstrom units, exposing it for one-third second. They could demonstrate no consistent electrophoretic changes in the plasma and no harmful effects on recipients of it. They failed to present any data on hepatitis-virus survival, merely accepting the earlier work of Oliphant[107] that this amount of irradiation should be viruscidal.

Gellis and his associates,[108] however, used 15 human volunteers and demonstrated that heating serum albumin at 60°C. for ten hours (routine procedure with salt-poor albumin) actually inactivated known infective virus added to the albumin samples after fractionation.

Prophylaxis and treatment with serum gamma globulin (effective for infectious-hepatitis prophylaxis[109–112]) has been quite disappointing. Grossman et al.[113] treated alternate casualties returning to the United States from the European theater.

Those treated and controls had received blood or its derivatives. Three hundred and eighty-four patients were given 10 cc. of gamma globulin intramuscularly and 10 cc. more thirty days later. The incidence of hepatitis among the 384 control patients was 11.5 per cent in the next six months, whereas that in the treated group was only 2.9 per cent. Two subsequent investigations unfortunately failed to repeat this. Robinson and his co-workers[114] gave one injection of 10 cc. of gamma globulin to 523 Army patients, with resulting hepatitis in 2.1 per cent. The incidence in 449 controls was 2.0 per cent. Duncan et al.,[115] in a similar experiment, obtained an incidence of 1.2 per cent in 2406 treated patients and 0.9 per cent in 2374 controls. They observed, however, that Grossman had used two prophylactic injections instead of one, and that in their series the onset of the acute phase was delayed an average of eighteen days among the treated patients who contracted hepatitis.

Besides this difference in response to gamma globulin, Neefe et al.[116] with human volunteers and Gauld[117] in a field epidemic of hepatitis in North Africa* showed that there was no cross-immunization between the two agents. Since there is no cross immunity, since the epidemic virus attacks younger age groups and since the incubation periods vary (infectious twenty-one to forty and serum sixty to one hundred and eighty days[118]) many have sought to explain the survival and transmission of the agent of serum hepatitis, other than by parenteral transfer. Truelove and Hogben[119] suggest the possibility of a sperm-placenta transfer.

In the face of this evidence, the Committee on Blood and Blood Derivatives of the American Red Cross made the following recommendations to the Council on Pharmacy and Chemistry of the American Medical Association[120]: that plasma be used only when nothing else is available; that the past history of all jaundice patients be carefully investigated; that no blood donors be accepted who have had jaundice or lived with a patient with jaundice or received any parenteral injections of blood or its derivatives in the preceding six months. Until a proved reliable method for inactivating the hepatitis agent is presented, these recommendations should be carried out.

Use

Lozner et al.[121] report on the safety of liquid plasma stored at room temperature for three years. As a colloidal solution, it is quite satisfactory but electrophoretically shows complete destruction of fibrinogen and gamma globulin and some reduction in beta globulin with a slight increase in osmotic pressure. Destruction of gamma globulins and associated antigens gives it an even lower reaction rate than that of dried plasma.

Probey[122] showed that drying to less than 1 per cent moisture made plasma noninfective even when it contained *Treponema pallidum*.

The question of the danger of mercurial preservatives remains unsettled. McNally[123] recommended a maximum of 4 liters of plasma containing mercurial preservatives in a short time to a patient without kidney damage, and less if damage is present. Individual tolerance is quite variable, however, as shown by Leamon's[124] patient who received 437 injections of mercupurin in five and a half years for congestive heart failure and yet showed no kidney damage at autopsy.

Although the use of concentrated plasma has never been too successful, two recent reports are of interest. Cleland[125] successfully treated traumatic pulmonary edema with 400 to 800 cc. of triple concentrated plasma. Fearnley[126] kept a patient with subacute hepatic necrosis free from ascites for eight months using 25 units of twice-concentrated plasma.

Plasma Fractionation

Method

The background, history and development of the plasma-fractionation program have been adequately recorded,[9–12, 127–140] the definitive documentation being now available.[9] Briefly outlined, they are as follows.

Early in World War II, global supply lines and overloaded transportation systems indicated that an effective, stable agent of small bulk for combating shock would be highly desirable, particularly for the Navy. Eventually the Army, Navy, National Research Council, Committee on Medical Research of the Office of Scientific Research and Development, Department of Physical Chemistry, Harvard Medical School, National Institute of Health, Massachusetts Department of Public Health, American Red Cross and seven commercial biologic laboratories collaborated to solve this problem. Until a better substitute was found, it was decided to separate the components of plasma and concentrate the albumin that was chiefly responsible for osmotic pressure, most stable, least antigenic and less viscous. Utilizing differences in solubility dependent on reaction, temperature and salt, protein and precipitant concentrations, Cohn selected ethanol as the precipitant best adapted to commercial use. As Hardy[141] and Mellanby[142] had shown in 1905, ethanol does not denature protein at temperatures below 0 to −5°C. It can also be removed and recovered by vacuum drying (lyophilizing).

Originally five groups of more or less similar proteins were separated (Fractions I to V), the last being albumin. Later the second and third groups

*The incidence of epidemic hepatitis in January, 1944, among three groups of soldiers was as follows: 438 who had had yellow-fever-vaccine jaundice in 1942, 11.6 per cent; 7900 who had been vaccinated in 1942 without jaundice, 4.8 per cent; and 2500, who had not been vaccinated, 4.5 per cent.

were removed together (Fraction II plus III) and subfractionated, Fraction IV was removed in two steps, and a residue, Fraction VI, was left after albumin removal. Details of the method are adequately reviewed by Mulford.[12] Table 1 summarizes the variations in chemical conditions used for separation, and the electrophoretic composition of the principal fractions. Table 2 lists the components of the various fractions with relative amounts and specific interactions. Table 3 gives dimensions of the proteins obtained and of several suggested substitutes. Improved methods have produced at least twenty-seven components, and the old fraction-subfraction nomenclature is losing its usefulness. Plans are underway to revise the fractionation method entirely, precipitate the albumin and lipoproteins first, obtain better products and greater yields, designate the components by their chemical names and abandon the Fraction designations.[144] The preparation of so many fractions, with diverse uses, has exceeded in importance the original purpose of fractionation: to obtain an agent for combating shock. Each component now has a variety of uses.

TABLE 1. *Separation and Electrophoretic Composition of Principal Fractions of Human Plasma by Method 6.**

FRACTION	CONDITIONS OF SEPARATION					ELECTROPHORETIC COMPOSITION†					
	REACTION	IONIC STRENGTH	TEMPERATURE	ETHANOL	PROTEIN IN SYSTEM	ALBUMIN	ALPHA	BETA	GAMMA	FIBRINOGEN	TOTALS
	pH	* Us*	*°C.*	*%*	*gm./liter*	*gm./liter*	*gm./liter*	*gm./liter*	*gm./liter*	*gm./liter*	
Plasma	7.4	0.16	—	—	60.3	36.3	9.2	10.6	7.2	2.5	65.8
I	7.2	0.14	−3	8	51.1	0.2	0.3	0.5	0.3	2.1	3.4
II + III	6.8	0.09	−5	25	30.0	0.8	1.1	9.1	7.0	1.0	19.0
IV-1	5.2	0.09	−5	18	15.8	0	4.5	0.5	0.1	0	5.1
IV-4	5.8	0.09	−5	40	10.1	0.9	2.7	2.2	0	0	5.8
V	4.8	0.11	−5	40	7.5	29.9	1.3	0.3	0	0	31.5
VI	4.8	0.11	−5	40	0.2	0.8	0.2	< 0.1	0	0	1.0
Totals	—	—	—	—	—	32.6	10.1	12.6	7.4	3.1	65.8

*Adapted from Brand and Edsall.[12]

†Estimated in plasma. The figures in the top row are for measurements directly on plasma; those in the bottom row are summations from the distribution in the plasma fractions, multiplying by the appropriate factor for the percentage of total plasma protein represented in the fraction.

Use of Fractions

Fibrinogen (Fraction I-2) and Thrombin (Fraction III-2). These clotting globulins were combined by Bering[145] into a light, sterile absorbable *fibrin foam*, which was originally used as a hemostatic agent in neurosurgery[11, 146] and more recently in other fields. Bailey et al.[147] found it to be an effective agent for stopping oozing and venous bleeding in 240 patients, including hemophiliacs, in whom it caused only slight tissue reaction. It was especially useful in tumor beds and on the cut surface of parenchymatous organs. Fallon and Croskery,[148] in 236 trials, also found fibrin foam valuable in general surgery. It can be employed with penicillin or sulfonamides and in infected cavities,[149] but has no effect on arterial bleeding. Kepl and Ahlquist[150] report the successful use of foam and thrombin instead of pleura to cover a bronchial stump after lobectomy. Quinby[151] found it to be a useful pack in 40 suprapubic prostatectomies.

There is now considerable literature comparing fibrin foam with oxycellulose[152, 153] and gelatin sponge.[154] Results are essentially the same[155] in neurosurgery,[156, 157] vascular and organ defects,[158] closure of bronchial wounds,[159] obliteration of dead spaces in orthodontics,[160] sinus and mastoid surgery[161] and nephrostomy[162] and prostatectomy.[163, 164] Buchman and Blair[165] believed, however, that both oxycellulose and gelfoam interfered with the healing of fractures and bone cavities more than fibrin foam did and have abandoned all three for dead-space obliteration. This might be due to the high acidity of oxycellulose, which Olwin and Wahl[166] found inactivated thrombin and could not be successfully buffered. The other two did not interfere.

Fibrin film prepared by Ferry and Morrison[167] from fibrinogen and thrombin was first used as a dural substitute.[11, 168] More recently it has been used to repair perforations in tympanic membranes and nasal septums.[161] The film has been studied considerably, and its physical characteristics can be altered to provide a "tailor-made" rigid or pliable substance of slow or fast absorption time with minimal tissue reaction.[169–174] Swenson and Gross[175] have utilized this material in the form of rigid tubes for blood-vessel anastomosis with a non-suture technic. With one end of a severed vessel threaded through the tube, that end is then turned back as a cuff over the tube, and this cuffed end inserted into the other severed blood-vessel end, which is then held in place by a ligature around everything. In 27 dogs whose vena cava or jugular veins were severed and thus reunited all survived, no thromboses occurred, and all evidence of the tubes had disappeared in six or seven weeks. Arteries have also been joined in this manner.

Fibrinogen and thrombin injected separately into the renal pelvis, allowed to clot and removed by pelvotomy have brought out all the tiniest stones in 28 of 36 cases reported by Dees.[176]

Fibrinogen intravenously has been successfully used by Diamond et al.[144] to combat congenital hypofibrinogenemia.

Antihemophilic globulin (Fraction I). The antihemophilic activity of Taylor's unidentified globulin has been found in Fractions I, II plus III and IV-1.[177–179] Its nature is still unknown, since no electrophoretic or chemical difference can be detected between normal and hemophiliac plasma or fractions, but it is distinct from fibrinogen, persisting after all clotting ability has been destroyed.[178] With potent preparations 400 mg. of Fraction I in a 20-cc. solution given intravenously has controlled hemophiliac bleeding especially if used with fibrin foam and thrombin locally. Dutch workers have obtained similar results using a fibrinogen solution prepared by ether precipitation.[180]

Gamma globulin (Fraction II). Most antibodies are selectively concentrated in this fraction,[181] and it has been used in prophylaxis and modification of measles with considerable success by groups headed by Stokes,[182, 183] Janeway,[138, 184] Rutstein[185] and others.[186, 187] The measles antibodies are concentrated about twenty-five times those of pooled adult plasma and if given before the sixth day after exposure will usually prevent (dose 0.08 to 0.1 cc. per pound of body weight) or modify the disease (dose 0.02 to 0.025 cc. per pound), giving a permanent protection. Equally satisfying results follow the prophylactic use of gamma globulin in epidemic hepatitis, especially if this substance is administered more than six days before onset of symptoms as shown by the groups of Stokes[109, 110, 183] and Paul.[111] Dosage varies from 10 cc. per adult to 0.15 cc. per pound of body weight in children. Unfortunately, it seems ineffective against homologous serum hepatitis,[114, 115] despite earlier encouraging work.[113]

TABLE 2. *Protein Components of Human Plasma Separated and Concentrated in Diverse Fractions.**

PROTEIN COMPONENT	ESTIMATED AMOUNT IN 100 GM. PLASMA PROTEIN	CONCENTRATED IN FRACTION†	APPROXIMATE ISO-ELECTRIC POINT	SPECIFIC CHEMICAL INTERACTION
	gm.			
Fibrinogen	4.0	I-2	5.3	Thrombin
Nonclottable protein, insoluble at low temperature	0.15	I-1		
Antihemophilic globulin‡		I		
Antibody gamma-globulins: Diphtheria antibodies‡	(0.001)			
Measles antibodies‡				
Mumps antibodies‡				
Streptococci antitoxin‡	11.0	II	7.3	Antigens
Influenza antibodies‡				
Pertussis antibodies‡				
Typhoid "H" agglutinins‡				
Antibody euglobulins: typhoid "O" agglutinins‡		III-1	6.3	Antigens
Isoagglutinins: anti-A, anti-B‡	(0.03)	III-1	6.3	Incompatible red blood cells
anti-Rh antibodies‡				
Complement components: C'1	0.4	III-2§		
C'2		IV§		Antigen-antibody complex
Eynzme precursors: Prothrombin	0.3	III-2		Thromboplastin
Plasminogen		III-3		Streptokinase
Serum enzymes: Thrombin‡		III-2	4.8	Fibrinogen
Plasmin‡		III-3		Proteins
Amylase‡				Starch
Lipase‡				Lipid
Peptidase‡		IV		l-Leucylglycylglycine
Phosphatase‡ (alkaline)		IV§		Phosphoric acid monoesters
Esterase‡	0.02	IV-6	4.5	Acetyl choline, ethylbutyrate
Metal-combining beta1-pseudoglobulin: crystallized	2.5	IV-7	5.6	Iron and Copper
High molecular weight (S = 7	2.0	III-0		
Beta-1-globulins (lipid-poor) (S = 20	1.0	III-0		
Iodoprotein‡¶		IV-6		
Thyrotropic hormone‡		IV-4		
Glycoproteins: Alpha-1-glyco-pseudoglobulin	0.7	IV-6	4.9	
Alpha-1-mucoid globulin	0.5	IV-6	4.9	
Lipoproteins: Beta-1; 75 per cent lipid-containing "X"-protein	5.0	III-0	5.6	Estriol, carotenoids, and other steroids
Alpha-1; 35 per cent lipid-containing protein	3.0	IV-0	5.2	Steroids
Blue-green pigment alpha-globulin		IV-2		
Bilirubin-containing alpha-1-globulin¶	0.05	V-1	4.7	Diazo reaction
Albumin: crystallized with mercury		V	4.9	Mercury, decanol
Albumin: crystallized with decanol	50.0	V	4.9	Fatty acids, bile salts, many dyes and drugs

*Adapted from Cohn.[18]

†When purified chemical components have been separated from fractions they have not been given new fraction numbers. In that case, the fraction number refers to the starting material for the separation of the component.

‡These components represent but small proportions of the fraction and subfraction, and their properties cannot, therefore, be deduced from those of the concentrates in which they have been separated.

§These components have not been tested for since revision of the fractionation process.

¶Albumin binds more bilirubin than the bilirubin pigment globulin in Fraction V-1 and more iodine than has been found in Fraction IV-6.

The evidence on this point remains conflicting, however.

Ordinary gamma globulin is ineffective against mumps. When prepared from mumps convalescent plasma, it is useful in preventing orchitis in adult males.[185, 187] Although gamma globulin has been reported to protect against chickenpox,[188] controlled studies have not confirmed this.[189]

Tremendous doses (20 to 100 cc. intramuscularly) were ineffective in treating 56 poliomyelitis patients in a New York epidemic when compared with 55 alternate controls.[190] The extremely low attack rate of poliomyelitis has prevented any adequate trial of prophylaxis; very large groups would have to be inoculated to provide statistical data.

Adams and Smith[191] divided students at the University of Minnesota into two similar groups on the basis of previous history of colds. The group receiving 6 cc. of gamma globulin in October and 4 cc. monthly for six months reported 77 colds (10 severe) as opposed to 132 (28 severe) in the controls. This has not been confirmed as yet.

Because of the grave effects on the fetus of maternal rubella in the first trimester as originally reported by Gregg,[192] gamma-globulin prophylaxis should be considered. No satisfactory series has been reported.[183]

All injections of gamma globulin must be given intramuscularly because of the occasional presence of a depressor substance[189] in some preparations. Although marked anticomplementary activity by gamma globulin has been observed in vitro,[193] none has been demonstrated in vivo.[194] A better preparation may result from the work of Deutsch et al.[195] showing that peptic digestion cleaves the gamma globulin molecule without diminishing antibody activity, thus improving absorption and effecting further concentration.

The possible origin of gamma globulin[196] from lymphocyte cytoplasm regulated by the pituitary adrenal secretion and adrenal cortical activity has not been definitely established.[197]

Isoagglutinins (Fraction III-1). If plasma from Group A and B donors is pooled separately, anti-A and anti-B isoagglutinins of high titer and specificity can be obtained.[198] This, however, provides only small amounts of anti-A because of the low percentage of Group B donors encountered. Melin[199] overcame this difficulty by ingeniously combining blood from "O" and "B" donors in such proportion that the anti-B agglutinin of the "O" plasma is quantitatively removed by the "B" cells, leaving an adequate supply of potent anti-A material. Because the fractionation method concentrates agglutinins five to eight times it has also been possible to prepare potent anti-Rh typing serum from pools of poorly immunized Rh— persons with a titer too low for ordinary use.[198, 200]

Iron-binding globulin (Fraction IV-7). After Holmberg and Laurell's[201] demonstration that serum iron is transported by an iron-binding protein that is normally one third saturated, Schade and Caroline[202] located this activity in Fraction IV-3,4 (later refractionated as IV-7), where it was identified[203, 204] as a β_1 pseudoglobulin of 90,000 molecular weight, binding 2 molecules of iron per molecule of globulin (0.38 to 1.25 gamma of Fe^{++} per milligram of globulin). Clinical investigation by Wintrobe et al.[205] and Rath and Finch[206] confirmed the ability of this fraction to transport iron. The latter's figures on 20 normal persons and 86 patients check closely with Laurell's[207] results: a normal serum iron-binding capacity of 314 microgm. per 100 cc. with normal iron content of 102 microgm. per 100 cc., compared with Laurell's capacity of 315 microgm. per 100 cc., 34 per cent saturated. The capacity

TABLE 3. *Estimates of the Dimensions of Certain Plasma Proteins and Suggested Blood Substitutes.**

SUBSTANCE	MOLECULAR WEIGHT	DIMENSIONS OF ELLIPSOIDAL MODEL		INTRINSIC VISCOSITY
		LENGTH	DIAMETER	
	molecules	*angstrom units*	*angstrom units*	$H \times 10^3$
Serum albumin (human)	69,000.0	150.0	38.0	4.2
Alpha-1-globulin (Fraction IV-1)	200,000.0	300.0	50.0	6.6
Beta-1-globulin (Fraction IV-7)	90,000.0	190.0	37.0	5.5
Beta-1-globulin (Fraction III-0)	1,300,000.0	185.0	185.0	4.1
Gamma-globulin (Fraction II)	156,000.0	235.0	44.0	6.0
Fibrinogen (human)	400,000.0	700.0	38.0	25.0
Serum albumin (bovine)	69,000.0	150.0	38.0	4.2
Hemoglobin (human)	68,000.0	36.0†	64.0†	3.8
Globin (human)	34,000.0	118.0	28.0	7.0
Gelatin: undegraded	46,000.0	330.0	17.0	47.0
P 20 type	36,000.0	260.0	17.0	36.0
P 180 type	19,000.0	140.0	17.0	18.0
Isinglass (degraded)	29,000.0	240.0	16.0	24.0
Glutamic acid polypeptide	15,000.0	260.0	11.0	24.0
Glucose	180.0	9.5	6.5	4.0
Chloride ion	35.5	3.6	3.6	—
Sodium ion	23.0	1.9	1.9	—
Erythrocyte (human)	—	24,000.0	86,000.0	4

*Adapted from Janeway and Oncley,[14] Oncley, Scatchard and Brown[185] and Cohn.[191]

†From x-ray studies indicating that the hemoglobin molecule is a platelet having the approximate dimensions 36 x 64 x 48 angstrom units.

is unaffected by amount of iron intake. In iron-deficiency anemias, the serum iron is decreased, and the unsaturated and total binding capacity increased. All decrease in anemias of infection. In hemochromatosis, the percentage of saturation rises considerably. Studying 25 newborn infants and their mothers, Laurell[207] was able to show that the iron-binding protein did not pass through the placenta freely whereas the iron did (mothers, serum-iron 80 microgm. per 100 cc. and total binding capacity, 446 microgm. per 100 cc.; newborn infants, serum iron, 146 microgm. per 100 cc. and total binding capacity, 226 microgm. per 100 cc.). Apparently, copper is bound in the same fashion by this protein.[204]

Miscellaneous. After Szego and Roberts[208] demonstrated that two thirds of the total circulating estrogen in normal, pregnant or gonadotropin-injected cows, rabbits and women was closely associated with a plasma protein fraction, they were able to locate most of this activity in the 75-percent-lipid-containing β_1 "X" protein of Fraction III-0.[209] The plasmin that Christensen[210] considers responsible for fibrinolysis* is found in Fraction III-3. The choline activity of serum occurs in Fraction IV-6.[212]

*Possible mechanism: plasminogen + streptokinase = plasmin that is inactive as long as neutralized by antiplasmin.[211]

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

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CASE 34411

PRESENTATION OF CASE

First admission. A twenty-eight-year-old married nulliparous housewife entered the hospital complaining of pain in the left lower abdomen.

She had had dysmenorrhea for several years. In the past she had had an appendectomy and uterine suspension, at which time endometriosis was found. There was a family history of tuberculosis, but the patient's chest films were consistently normal. Recently during her periods she had taken large numbers of anacin tablets and on one occasion the white-cell count fell to 3000. Examination revealed a small cervix and a large uterus, which was thought to contain a large fibroid. An operation was performed and a fibroid, 5 by 5 by 4 cm., was removed. Also removed were the left tube and ovary and a follicle cyst of the right ovary. Many adhesions were present in the peritoneal cavity.

Second admission (three years later). Following operation the patient was placed on testosterone therapy for severe dysmenorrhea. She had marked but not complete relief. She had extensive studies for sterility. Another fibroid appeared to be growing in the uterus. Air insufflation at 200 mm. of mercury produced no shoulder pain. Six months before admission a salpingogram showed complete filling of the right tube and of the proximal stump of the left. There was no escape of lipiodol into the peritoneal cavity.

For two and a half weeks before admission the patient complained of pain low in the back and crampy pain in both lower quadrants of the abdomen, associated with some nausea and a brownish vaginal discharge. Her period, which was three weeks late, commenced two days before admission and was normal in all respects. She stated that she had had delayed periods, brown discharge and similar pain with periods before, but the pain had not been quite so severe. There were no gastrointestinal, genitourinary or cardiorespiratory symptoms, or breast changes.

Physical examination revealed slight tenderness deep in the right lower quadrant, and on pelvic examination the cervix was firm, smooth, and somewhat tender on motion. The uterus was enlarged, apparently with a fibroid. There was a tender, ill defined mass in the right vault, and the pulsations of the right uterine artery were noticeably increased.

The temperature was 99.8°F. (Urine was taken for an Aschheim–Zondek test before admission, but the animals died before the reaction could be read.)

The day after admission an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. LANGDON PARSONS: One thing that intrigues me is the inaccuracy of pelvic examination at various times. First, the large uterus was *thought* to contain a large fibroid; at another time the fibroid *appeared* to be growing in the uterus; then the uterus was enlarged, *apparently* with a fibroid.

There is no definite statement that it was ever present.

We have to explain the presence of this mass in the left lower abdomen. That location is the graveyard of all gynecologic diagnoses. It is very difficult to make a diagnosis of a lesion in the left lower quadrant because of the presence of the sigmoid. That is where we "come a cropper" so many times. The patient was operated on for dysmenorrhea, and endometriosis was said to have been found. Apparently it was an external form of endometriosis. There is no mention of involvement of the ovary, and nothing is said about what was done at the original operation. I do not know whether the tube and ovary were removed and showed evidence of endometriosis.

DR. TRACY B. MALLORY: They were not removed. The surgeon reported that there was peritoneal endometriosis but did only a routine appendectomy.

DR. PARSONS: There was a family history of tuberculosis. The chest films were normal. To go along with the possibility of tuberculosis of the tube is the fact that at one time the white-cell count was 3000, although it was said to have been associated with the taking of anacin tablets. It is interesting that every now and then one finds a patient who has a leukopenia at the time of her period. Possibly this was associated with the anacin tablets; on the other hand, she may have had a marked fall in the white-cell count at the time of the period. The fact that she had normal chest films does not necessarily rule out tuberculosis of the tube. The thing that is most likely to rule it out is the subsequent operation. The left tube and ovary and a follicular cyst of the right ovary were removed, and no mention of tuberculosis was made at that time. Unilateral tuberculosis is unlikely. Do we have any note of the pathology at the time of the removal of the left tube and ovary at the second operation?

DR. MALLORY: In addition to the fibroid and the follicular cyst mentioned there was a ruptured corpus hemorrhagicum, but no endometriosis could be identified. The tube showed no evidence of tuberculosis.

DR. PARSONS: That has some bearing on the rest of the picture. There is one other pathologic entity that closely simulates tuberculosis of the tube. Air insufflation was done, followed by a salpingogram. In a number of cases in this hospital I have been grossly fooled. Lipiodol injected into the tube and uterus has produced a granulomatous type of lesion within the tube, and when these lesions develop on the outside of the tube they closely simulate tuberculosis. I do not believe one can distinguish it grossly, and it is very difficult for the pathologist to tell whether this lesion is tuberculosis of the tube or whether it is a granuloma associated with foreign-body reaction to the lipiodol. So that is a possibility.

Endometriosis was mentioned at the original operation, and the patient was subsequently given testosterone therapy for dysmenorrhea, with partial relief. One would expect no more than partial relief from testosterone with the type of endometriosis that is external. If the testosterone inhibits the pituitary gland and thereby affects the uterine musculature, partial relief from the dysmenorrhea might occur. I assume that is why she was given it.

I think we have been, in the past, a little bit too ready to take out ovaries in association with endometriosis in younger girls. I think it is possible to be more conservative. The endometriosis can be resected out of the ovary and a fair amount of normal tissue left. However, it is difficult to tell grossly whether one is dealing with a corpus hemorrhagicum or a chocolate cyst due to endometriosis. There is one factor about the diagnosis of endometriosis that puzzles me. With endometriosis the tubes are invariably open, and yet in the tests for sterility, the air did not pass readily and the lipiodol subsequently given met a block. The record does not say that there was block; it simply says "complete filling," but when the x-ray film was taken twenty-four hours later it failed to show passage of lipiodol in the peritoneal cavity. Three years before when she came into the hospital this tube must have been open. It is not invariable, but in 276 out of 283 cases of endometriosis that Sampson* has reported, the tubes were open.

I think the adhesions present in the pelvis at the time of the second operation may well be explained by the presence of endometriosis, but again one would expect that to be ovarian. Adhesions do not occur with external implants on the peritoneum as in ovarian endometriosis.

Everything is "rigged" against pregnancy in this patient, and yet that is what I think she had. In the first place, the air insufflation is said to have shown a block in the only tube that she had. After lipiodol injection no droplets were seen in the peritoneal cavity when the film was taken subsequently. Nevertheless, she came in complaining of pain in the lower back, crampy pain in both lower quadrants associated with nausea, and a brownish vaginal discharge. I interpret this as a delayed period. She was said to have had a period that was normal in all respects two days before entry, but it is possible, of course, that this was not a normal period at all. I would assume death of the ovum within the tube and consequent bleeding, which might closely simulate a normal period. She had had some brownish vaginal discharge and some crampy lower abdominal pain. On examination the cervix was said to be tender on motion, and an ill defined mass could be felt in the right lower quadrant. The left tube and ovary had been removed. One interesting fact is that definite pulsations were felt in the right uterine artery. We do

*Sampson, J. A. Peritoneal endometriosis due to menstrual dissemination of endometrial tissue into peritoneal cavity. *Tr. Am. Gynec. Soc.* **52**: 171-218, 1927.

not know how often such pulsations are felt with ectopic pregnancy. As I say, everything has conspired against pregnancy. The fact that there were no breast changes is against pregnancy. She had had one follicular cyst, which required removal. This could have been another cyst with infarction, but I am inclined to think that it was an ectopic pregnancy.

DR. JOE V. MEIGS: I did the second and third operations. When I operated the first time the tube and ovary on the left side were included in a mass with a large fibroid, which I removed. The consensus at that time was that it was necessary to remove the left tube and ovary as well as the fibroid. I thought that it was endometriosis and took a suspicious area for biopsy, but according to the report that was sent back I was wrong, although I still thought that she had some. She had a good tube and ovary on the right side. Her husband's sperm count was 60,000,000, which Dr. Ingersoll thought was at the lower edge of normal. We would classify such a patient with a fibroid and endometriosis in the low fertility group and would not expect her to become pregnant. When the recent episode developed she thought that she was miscarrying and Dr. Morris, who went to see her, was of the same opinion. We found the uterus enlarged, with many intramural fibroids, and decided to do a hysterectomy.

CLINICAL DIAGNOSIS

Endometriosis.
Ectopic pregnancy?

DR. PARSONS'S DIAGNOSIS

Ectopic pregnancy.

ANATOMICAL DIAGNOSES

Tubal pregnancy.
Endometriosis of peritoneal surface of uterus.

PATHOLOGICAL DISCUSSION

DR. MALLORY: The sections from the tube did show recognizable chorionic villi. There was a very marked decidual reaction in the endometrium of the uterus. At the previous operation we failed to find the endometriosis that Dr. Meigs expected, in spite of the fact that we examined many sections. On this occasion he sent the specimen over with the familiar safety pins in it, and on cutting our sections from those areas we found the endometriosis.

CASE 34412

PRESENTATION OF CASE

A thirty-four-year-old housewife entered the hospital complaining of pain in the left chest.

Five months prior to admission the patient had had a "cold," with a temperature of 101 and 103°F. at night, without chills. The episode was associated with "gnawing" pain in the right upper quadrant, unassociated with eating or breathing and of an intermittent character. She had received penicillin once and sulfadiazine. X-ray films of the chest were reported normal. Two weeks later pain developed in the left upper quadrant, aggravated by deep breathing and associated with a dry morning cough. The pain gradually became more severe and extended to include the left paravertebral area. She was seen in the Out-Patient Department. X-ray examination showed an area of pneumonitis present in the posterior basilar segment of the left lower lobe and possibly a small amount of fluid in the left costophrenic sinus. The remaining lung fields were clear. The heart and vessels appeared normal. A diagnosis of pneumonitis with residual involvement of the left lower lobe was made. About one and a half months before admission another x-ray examination in the Out-Patient Department showed that the left lower lobe was slightly smaller and more dense than on previous examination. The diaphragm was adherent to the chest wall posterolaterally adjacent to this area. There was possibly a small amount of fluid also present. About one week before admission the patient was again seen in the Out-Patient Department. The left-chest pain, which had disappeared some time after the last visit, had recurred, had become continuous, and was of a pleuritic nature. Since the reappearance of pain, she had run a mild fever and had complained of some insomnia because of pain. At this time there was slight swelling in the left paravertebral region. A history of a weight loss of about 15 pounds since the beginning of the illness was elicited.

Physical examination disclosed a round area of swelling 10 cm. in diameter in the left paravertebral region at the level of the lower part of the thorax. There was considerable tenderness to percussion, with diminution of breath sounds and tactile and vocal fremitus over this area. There was tenderness of the spleen on deep palpation. The liver edge was palpated one fingerbreadth below the costal margin in the epigastrium and was firm and nontender.

The temperature was 100.8°F., the pulse 94, and the respirations 20. The blood pressure was 98 systolic, 65 diastolic.

Examination of the blood revealed a hemoglobin of 9.8 gm. and a white-cell count of 16,000, with 88 per cent neutrophils. Urinalysis gave a specific gravity of 1.018 and was negative for sugar, albumin and bile. A tuberculin test in a dilution of 1:10,000 was negative.

X-ray examination showed that the process in the left-lower-lung field had increased somewhat and was considerably larger than it had been originally. It was difficult to be certain whether it was primarily within the lung or pleura, but it seemed more likely that the bulk of the disease was in the lung. There was also soft-tissue thickening along the left paravertebral margin of the lower vertebras, which was perhaps slightly more than at the time of previous study. The lumbar spine was not definitely abnormal.

An operation was performed on the fifth hospital day.

Differential Diagnosis

Dr. Helen S. Pittman: I understand that the only x-ray film available is the one taken in the Out-Patient Department one week before admission. Is that correct?

Dr. James J. McCort: Yes.

Dr. Pittman: So that we are missing an outside film taken twelve months before admission — said to be normal — and the Out-Patient Department film taken two weeks after, which was reported to show an area of pneumonitis in the posterior basilar segment of the left lower lobe and possibly a small amount of fluid in the left costophrenic sinus. Then we have the next one taken a week before admission. May we see that, Dr. McCort?

Dr. McCort: The area of pneumonitis described is present in the posterior basal segment of the left lower lobe. This segment also shows partial collapse, and the left leaf of the diaphragm is elevated. A small amount of fluid is present in the left costophrenic sinus. The paravertebral thickening may be caused by a small amount of fluid in the left inferoposterior costomediastinal space. Soft-tissue thickening over the left lateral margin of the chest wall can be seen, and the normal, clear-cut outline of the subcutaneous fat line is lost on that side. The lung fields are otherwise clear. The heart and vessels are normal.

Dr. Pittman: The upper edge of the liver is down a little bit, perhaps one fingerbreadth. It does not necessarily indicate increased size, does it?

Dr. McCort: No.

Dr. Pittman: We are missing the first film taken on admission to the Out-Patient Department and the one taken in the house that shows this process reported in the left-lower-lung field to have increased somewhat and to be considerably larger than in the first film. It is difficult to be certain whether the process is primary in the lung or pleura, but more likely it is in the lung. The soft-tissue thickening along the paravertebral margin is perhaps slightly more marked.

I am having trouble discussing this case because I can make only one thing out of it and I think it is dangerous to have only one idea as soon as one reads a protocol. One should, I suppose, always think of a neoplasm. And this time I would think of neoplasm to exclude it. It does not seem to me that this is the history of neoplasm or that the x-ray films suggest any of the common features of neoplasm. And I am throwing neoplasm out now permanently.

The next thing in the history, which I suppose should get a moment of attention, is the story that the pain at the onset was in the right upper quadrant and was "gnawing," although it was unrelated to breathing or eating. A "gnawing" pain always makes one think of ulcer, but I am throwing that out because it seems to me that the idea that the chest process was anything secondary to the stomach is perfectly fantastic. I always remember a case of empyema that I saw many years ago when I was a house officer that was secondary to perforated ulcer, but I cannot make such a diagnosis fit here at all.

Then we come down, it seems to me, to infection. Infection has to be broken down into three groups: tuberculosis, the more common bacterial infections and the nonbacterial infections. This woman apparently had an acute onset. It was in

the chest, and therefore we should think about tuberculosis. Also, the fact that pleural pain was a rather constant feature should make one think about tuberculosis. It seems to me, going back to two weeks after the onset when the pain moved from the right upper quadrant to the left upper quadrant and was aggravated by deep breathing and associated with morning cough, that the pain was pleural — pain of pleural irritation. The tuberculin test at 1:10,000 dilution was negative. There is no history of sputum at any time, and so none was available for examination. I do not believe that tuberculosis needs to be considered any further.

So far as the common bacterial infections in the chest are concerned, this case began with a "cold," which according to our information was associated with fever and I suppose the common things that go with so-called "colds," and then a morning cough. At that time, when she came to the Out-Patient Department, two weeks after the onset, she had what was interpreted as pneumonitis with residual involvement in the left lobe. The initial x-ray film was said to be entirely clear. Did she have a pneumonia that only partially resolved? Did she have an empyema secondary to that pneumonia? I do not believe she did, and that brings me down to the other group of nonbacterial infections. And of that group I thought immediately of actinomycosis, and I cannot get away from it. We think now that one does not have to suck a straw or anything of that sort to introduce actinomyces into the body. They are present about the teeth and in the mouths of healthy people, at least part of the time, and they go down into the chest and start off the process, which I understand usually starts in the bronchi. I do not know anything about that stage of the disease from personal experience — that is just what I read. This woman started with signs of infection; she then developed a cough, having had some pleural pain (granted, before she had anything in the nature of a cough), and when she first appeared for x-ray study, she had a process in the left-lower-lung field and probably in the pleura. That went on for a bit, and then the symptoms subsided, which is perfectly commonplace in a story of an infection with actinomycosis. She then had a recurrence, having meanwhile come in with signs of chronic infection, such as fever, loss of weight, a significant anemia (9.8 gm. of hemoglobin) and a moderate leukocytosis (white-cell count of 16,000), with 88 per cent neutrophils. The urine was entirely normal. When she came in the process in the chest had increased. She had a round area of swelling, 10 cm. in diameter, on the left posteriorly at the level of the lower thoracic region. We know that actinomycosis invades the pleura; we know it invades the chest wall. She had a tender and palpable spleen; actinomycosis also invades the spleen, or one might have a tender area in the region of the spleen. One may have inflammation in the region above or below the diaphragm, with pleural involvement. So although I think she may have had disease in the spleen, I would not be surprised if she failed to show it. The only preoperative diagnosis that I can make is actinomycosis, and my assumption is that the operation performed was a needle biopsy of this area on the back of the chest or possibly exploration of it.

DR. JACOB LERMAN: When this patient first came on the ward the striking thing about the physical findings was the swelling of the chest wall. The lower half of the wall posteriorly was swollen, which was a little unusual in the presence of signs of empyema and pneumonitis. It is not mentioned in the record, but a needle was inserted into the chest wall by the resident, who was unable to obtain fluid. On the following day the swelling of the chest wall increased considerably. We assumed that he got into an area of pus. The service thought that it was necessary to rule out the various types of common organisms that infect the pleura following pneumonia, and, in addition, the uncommon types, particularly pneumonia due to Friedländer's bacillus with empyema. We discussed the possibility of mycotic infections of the chest wall, resulting from empyema. Unfortunately, we did not obtain a culture from the needle so that we were unable to settle the problem until operation was performed.

CLINICAL DIAGNOSIS

Unresolved pneumonia, with empyema.

DR. PITTMAN'S DIAGNOSIS

Actinomycosis.

ANATOMICAL DIAGNOSIS

Actinomycosis of chest wall.

PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: Will you tell us the operative findings, Dr. Gephart?

DR. F. THOMAS GEPHART: At operation this patient obviously had a fluctuant mass over the left lower chest posteriorly, and we had intended to drain the empyema at the same time. However, when we opened the lesion along the lower medial aspect, we encountered an estimated 100 to 200 cc. of cloudy pus, which had no unpleasant odor. We examined the cavity and found no areas of denudation of the ribs or any apparent break into the pleural cavity. So we felt that it would be better to pack this loosely and wall it off before sticking a needle into the chest to try to locate further fluid intrapleurally. We took cultures and a small amount of tissue for study.

DR. MALLORY: Have you anything to add, Dr. Miller?

DR. CARROLL C. MILLER: The only thing that I might add is that in operating we were cautious, particularly because of the location next to the vertebral column, thinking that it might possibly represent cold abscess with origin in the spine and that it might entail subsequent orthopedic maneuvers or possibly contamination of the spinal canal during a drainage operation. But we were more or less forced into operating — this lesion suddenly became so much larger and more tender. The patient was put on chemotherapy, I think two days before operation was done, and the chart actually looked better. In considering the chart alone we might have chosen to wait. After we saw the increased size and the tenderness of the process, we went ahead. I would like to make a statement from the therapeutic and diagnostic point of view — namely, to remind any listeners and subsequent readers of the advisability of being prepared to drain such a process immediately after tapping. This is said, not in criticism of the way in which the case was handled, because no pus was obtained, but so often we find that a diagnostic tap of the chest is done — maybe in the office or in the patient's bed — without preparation for operation. And we subsequently see a fulminating infection of the chest wall, which requires much more surgical treatment than if it had been immediately drained — by "immediately" I mean within a few hours.

DR. ROBERT H. BROWNING: This patient was seen in the Out-Patient Department, and one thing that is not mentioned in the history was that she was acutely tender over the spine, over the ninth, tenth and eleventh thoracic vertebras. A few days later when I saw her on the wards the tenderness had disappeared. I wonder if there was any evidence to indicate whether the thoracic spine was involved in the process either at operation or subsequently.

DR. MALLORY: The tissue removed for biopsy showed many clusters of actinomyces. I cannot tell you the extent of the anatomic involvement, or whether or not there was empyema or splenic or spinal involvement.

DR. GEPHART: A barium enema and an intravenous pyelogram were normal.

DR. MALLORY: Is the patient still in the hospital?

DR. GEPHART: Yes, she is still in the hospital. She has been afebrile and feels much better. The chest-wall cavity is closing down, although it has been open.

DR. PITTMAN: What are you treating her with?

DR. GEPHART: We started on penicillin, but after discussing the case with Dr. Kane we have taken several cultures and are trying to find out the sensitivity of this particular organism to various chemotherapeutic agents. At the present time we are also treating her with streptomycin.

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ELEVENTH HOUR

ON JUNE 20 Dr. Paul R. Hawley, speaking before the presidents and other officers of the various state medical associations, warned them that the moment of reckoning was at hand; that the hour was about to strike after which it would be too late for the medical profession in this country to determine its own future course. There is a strong and growing demand for national health insurance on the part of many powerful and resolute groups in the nation, and already the point has been reached "when the medical profession has the choice only of making a reasonable effort to meet the requirements of these large groups of consumers of medical care, or of watching the private practice of medicine in this country being rapidly strangled by either co-operative or Government medicine. No other alternatives are left. . . ."

This was a straightforward declaration by the chief executive officer of the Blue Cross and Blue Shield Commissions reiterating the important decision that faces medicine today. This decision is not whether there shall be effected an equitable distribution of medical care or whether a planned medical economy is desirable, but who shall bring about these changes.

Organized medicine, so-called (a name now changed to the noncommittal term "medical profession," a faint but fetid aroma having developed about the term "organized"), takes its steps always too reluctantly. It is the conservative bulwark of an ancient calling, and slow motion is almost implicit in its design, each year only those compromises with social reform being accepted that might have been considered progressive in the previous decade. Whether tardy approach is an utter necessity is another matter. Large bodies can sometimes move rapidly in the face of impending disaster.

This slowly moving body, however, is in the unfortunate predicament of being harassed by a confusion of committees and leagues and other groups, each, no doubt, completely worthy according to its principles, but whose insistence serves also to obscure the issue and to hide the light. They are the champions of private practice and a reformed status quo — the pillars of professional dignity; they are the advocates of universal and compulsory state medicine; they are, like General Hawley, the agents of a free system of prepaid medical care, delivered on an actuarial basis, which, today, might be considered as the middle lane of the road down which mankind is traveling.

In all justice the statement may be tentatively advanced and might still prove acceptable to a reasonable majority that this country is not yet ready for that compulsion of which there is already too much in the world. It must be remembered, however, that a compulsory Government insurance plan received strong support in the deliberations of the Section on Medical Care of the recent National Health Assembly.

The profession of medicine is not on as sure a footing with its public as might be wished; it has

so far done less than it could and than it should have done to ensure reasonably adequate medical care to all the people. It must remember that some of the criticisms directed toward it in this respect are in a sense a basic compliment. They are an acknowledgment that the services of medicine are considered by the people to be equally indispensable with the various accepted public services and, indeed, the very freedoms that are cherished — pure water and sanitation, police and fire protection, education, freedom of speech and of worship and the privilege of representative government.

If the medical profession does not assume active leadership, however, in assuring adequate distribution of its services, and that very shortly, its opportunity will be gone. It is the eleventh hour, and there are many that still stand idle outside the vineyard.

INTERNATIONAL HEALTH PROGRAMS

THE World Health Organization, now firmly established as a member agency of the United Nations, held its first World Health Assembly in Geneva in June and July, 1948. As a major part of the constructive work of the Assembly, provisional agenda for various international programs were drawn up and approved.

The Committee on Programme placed malaria control first on the list of recommended activities in view of the high prevalence of the disease, with hundreds of millions of cases and millions of deaths occurring each year. Next in order came maternal and child health, tuberculosis and venereal diseases. For further activities it was recommended that particular attention should be given to alcoholism, drug addiction and habit-forming drugs, hygiene of seafarers, influenza, nursing, nutrition, rural hygiene and schistosomiasis.

The proposed methods of attack under each major title are divided into specific procedures, the details of which are pertinent to that subject. These consist of a statement of the particular objectives to be sought, the development of a program of study, the provision of suitable assistance to governments and a program of action on the international plane.

So the world makes its slow progress, with men and nations of good will struggling for mutual benefits in the shadow of still stronger destructive forces. As Sisyphus toiling with his stone in Hades could never quite reach the top of the hill, so mankind, constantly frustrated, still lives in constant hope that at some time all men and all nations may bend their efforts toward a common goal.

COST OF THE COMMON COLD

AN ATTEMPT to arrive at a rough approximation of the cost to the American people of their common colds has been made by the statisticians of the Metropolitan Life Insurance Company,* who came up with the appalling figure of well over $1,000,000,000 a year. This figure was obtained by taking into account the data on incidence of the disease among wage earners, students and other special groups, according to the studies of many reliable investigators. The calculations ran somewhat as follows.

The average person suffers at least 2 colds a year or approximately 300 million annually for the entire country. The average duration of the simple cold is five days, giving a total of one and a half billion days of discomfort, decreased efficiency or disability. A conservative estimate of the time lost from work in this country is one day per employee per year, or more than sixty-million days lost in industry from this cause. Even at a low average of $7 a day, the result in wages alone is more than $420,000,000 annually.

The amount spent on medical care and drugs for the treatment of colds by the average family is impossible to arrive at, but it was assumed to be about $10 a year, or a total of about $400,000,000. No attempt was made to estimate the cost to employers resulting from the loss of production and disrupted routine, but it, too, must reach a considerable figure for the country as a whole.

These calculations led the Metropolitan's statisticians to arrive at the estimate of over $1,000,000,000 a year as the cost of the common cold to the American people. Although the common cold is generally considered to be a minor illness, they concluded that any disease in which the cost runs to such astronomical figures must be rated high in the list of enemies of the public health.

*Cost of common cold. *Statist. Bull. Metrop. Life Insur. Co.* **28** (No. 11): 6, 1947.

LIFE INSURANCE MEDICAL RESEARCH FUND

THE Life Insurance Medical Research Fund, organized in 1945 by a group of United States and Canadian life-insurance companies, with Dr. Francis R. Dieuaide as scientific director, has recently issued its third annual report. At the beginning of 1947 the Fund was contributing to the support of fifty-one research programs and nineteen research fellows. During the year this number was materially increased.

Present studies in which the Fund is interested are directed mainly toward the problems of heart disease, so important from the actuarial point of view, and are grouped under five general headings. These include studies on cellular metabolism of the heart and blood vessels, studies of the flow of blood, studies of kidney function and the development of hypertension, studies of the development of arteriosclerosis and studies of the causes of rheumatic fever.

Contributions by the life-insurance companies to research into the causes of premature death represent a sound investment on their part. Their profits are increased by human longevity, and, conversely, favorable results in the attainment of longevity should have their favorable effect on insurance premiums. It must still be borne in mind, however, lest universal longevity be achieved too rapidly, that the breadth of life may be more important than its length.

MISCELLANY

MEDICAL DIRECTOR OF LEVER BROTHERS COMPANY

The appointment of Dr. John J. Poutas, assistant medical director and chief of professional services in the New England office of the Veterans Administration, as medical director of Lever Brothers Company, Cambridge, has been announced.

NOTICES

SOUTH END MEDICAL CLUB

A meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, on Tuesday, October 19, at 12 noon.

Dr. Paul G. Myerson will speak on the subject "New Trends in Psychiatric Treatment."

This meeting will mark the beginning of the twenty-second year for the South End Medical Club. Physicians are cordially invited to attend.

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

A meeting of the New England Society of Anesthesiologists will be held in the Auditorium of Building A, Boston University School of Medicine, 80 East Concord Street, Boston, on Monday, October 18, at 8 p.m. The scientific program will be presented by Dr. Donald E. Hale, Cleveland Clinic, Cleveland, Ohio, whose subject will be: "Anesthesia for Neurosurgery: Use of hypotension."

Physicians and medical students are invited to attend.

JOSEPH H. PRATT DIAGNOSTIC HOSPITAL

Bennet Street, Boston
Lecture Hall, 9–10 a.m.

MEDICAL CONFERENCE PROGRAM

Friday, October 8 — Metabolic and Therapeutic Problems of Alkalosis. Dr. Charles H. Burnett.
Wednesday, October 13 — Journal Review.
Friday, October 15 — Renal Tuberculosis. Dr. Roger C. Graves.
Wednesday, October 20. Pediatric Clinicopathological Conference. Drs. James M. Baty and H. E. MacMahon.
Friday, October 22 — Rice Diet: Some experimental and clinical observations. Dr. William B. Schwartz.
Wednesday, October 27. Some Problems in Clinical Cancer Research. Dr. Fred Homburger.
Friday, October 29 — Some Special Features of Marked Mitral Stenosis. Dr. Edward F. Bland.

On Tuesday and Thursday mornings from 9 to 10 Dr. S. J. Thannhauser will give medical clinics on hospital cases. On the second and third Friday afternoons in October therapeutic conferences will be held from 2 to 4 with round-table discussion, Dr. Robert P. McCombs, moderator; the speakers will be: Dr. Somers H. Sturgis, whose subject will be "Sterility," and Dr. Fred Homburger, whose subject will be "Chemotherapy of Cancer." On the second and fourth Friday afternoons of each month Dr. Merrill Sosman will conduct x-ray conferences from 4 to 6. On Saturday mornings from 9 to 10 clinics will be given by Dr. William Dameshek. Medical rounds are conducted each weekday except Saturday by members of the staff from 12 to 1.

All exercises are open to the medical profession.

NEW ENGLAND DIABETES ASSOCIATION

The fall meeting of the New England Diabetes Association will be held in the Cheever Amphitheater of the Boston City Hospital on Wednesday, October 20, at 8:00 p.m.

The speaker of the evening will be Dr. George W. Thorn, whose subject will be "Some Fundamental Endocrine Relations in Diabetes."

After the clinical program there will be an important business meeting of the Association to discuss future policies.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, OCTOBER 14

FRIDAY, OCTOBER 15
*9:00–10:00 a.m. Renal Tuberculosis. Dr. Roger C. Graves. Joseph H. Pratt Diagnostic Hospital.
*9:00 a.m.–12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.
*12:00 m. X-Ray Conference. Margaret Jewett Hall. Mt. Auburn Hospital, Cambridge.

MONDAY, OCTOBER 18
*8:00 p.m. New England Society of Anesthesiologists, Auditorium of Building A, Boston University School of Medicine.

TUESDAY, OCTOBER 19
*12:00 m. South End Medical Club. Boston Tuberculosis Association, 554 Columbus Avenue, Boston.
*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.
*1:30–2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

WEDNESDAY, OCTOBER 20
*9:00–10:00 a.m. Pediatric Clinicopathological Conference. Drs. James M. Baty and H. E. MacMahon. Joseph H. Pratt Diagnostic Hospital.
*11:00 a.m.–12:00 m. Medical Clinic. Amphitheater, Children's Hospital.
*12:00 m. Clinicopathological Conference (Children's Hospital). Amphitheater, Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Combined Clinic by the Medical, Surgical and Orthopedic Services. Amphitheater, Children's Hospital.

*Open to the medical profession.

(*Notices concluded on page xiii*)